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ORIGINAL ARTICLE

Monocyte chemoattractant protein-1 and hypertension: An overview

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Abstract
Background: The association between hypertension and cardiovascular disease (CVD) has been increasingly studied through early inflammatory biomarkers. The monocyte chemoattractant protein-1 (MCP-1) is the main chemokine implicated in the inflammatory endothelial process, attracting monocytes and macrophages to the atherosclerotic plaque.
Methods: We reviewed the main observational studies that have analyzed serum MCP-1 in patients with hypertension regardless of CVD, relating them to target organ damage (TOD).
Results: As endothelial dysfunction continues and TOD accumulates, MCP-1 has been perpetuated at higher levels. The relationship between this chemokine and the increase in comorbidities, such as chronic kidney disease, dyslipidaemia, diabetes, and coronary artery disease, became clearer from the observational studies. However, patients with such morbidities use medications with potential anti-inflammatory effects.
Conclusion: There is no normal threshold of MCP-1 for the healthy population, nor a uniform curve pattern, due to a balance between genetic factors, age, gender, comorbidities, TOD, and anti-inflammatory effects of drugs. In fact, MCP-1 seems to have a promising role as a tool for further improvement in cardiovascular risk stratification, as prognostic studies have demonstrated an association with fatal and non-fatal cardiovascular outcomes, regardless of other clinical and laboratory predictors.

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PALABRAS CLAVE
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Inflamación;
Hipertensión resistente

Proteína 1 quimioatrayente de monocitos e hipertensión: generalidades

Resumen
Antecedentes: Se ha venido estudiando con mayor frecuencia la asociación entre hipertensión y enfermedad cardiovascular a través de los biomarcadores inflamatorios tempranos. La proteína 1 quimioatrayente de monocitos (MCP-1) es la principal quimioquina implicada en el proceso inflamatorio endotelial, que atrae monocitos y macrófagos a la placa aterosclerótica.
Métodos: Revisamos los principales estudios observacionales que han analizado la MCP-1 sérica en pacientes hipotensos independientemente de enfermedad cardiovascular, relacionándolos con el daño del órgano diana.
Resultados: A medida que prosigue la disfunción endotelial, y se acumula daño en el órgano diana, MCP-1 se perpetúa a niveles mayores. La relación entre esta quimioquina y el incremento de las comorbilidades, tales como la enfermedad renal crónica, la dislipidemia, la diabetes y la enfermedad arterial coronaria se hizo más evidente a partir de los estudios observacionales. Sin embargo, los pacientes con dichas morbilidades utilizan medicaciones con efectos antiinflamatorios potenciales.
Conclusión: No existe un umbral normal de MCP-1 para la población sana, ni un patrón de curva uniforme, debido al equilibrio entre factores genéticos, edad, sexo, comorbilidades, TOD y efectos antiinflamatorios de los fármacos. De hecho, MCP-1 parece tener un rol prometedor como herramienta de mejora futura de la estratificación del riesgo cardiovascular, ya que los estudios pronósticos han demostrado una asociación con los resultados cardiovasculares fatales y no fatales, independientemente de otros factores predictivos clínicos y de laboratorio.

Introduction

Hypertension is the leading cause of ischemic heart disease and stroke through a complex mechanism in which some stimuli can raise blood pressure (BP) independently or together namely: salt intake, angiotensin II (Ang II), aldosterone, and endothelin 1. These stimuli result in fluid and salt retention, increased systemic vascular resistance and sympathetic tone. Therefore, the kidney, endothelium, and central nervous system initially contribute to the high BP levels and perpetuate it.[1]

Inflammation is a restoring homeostasis process, repairing cell damage or tissue injury, but chronic and long-lasting inflammatory response can generate harmful effects and diseases.[2] Low-grade inflammation contributes to the development and progression of hypertension and cardiovascular diseases (CVD) through innate and adaptive immune activation.[3] The major agents of the innate immune system are macrophages, mastocytes, proinflammatory cytokines [like tumor necrosis factor-alpha (TNFα)], interleukins 1 and 6 (IL-1, IL-6), chemokines [such as monocyte chemoattractant protein-1 (MCP-1)], and acute-phase proteins [like C-reactive protein (CRP)]. Meanwhile, the adaptive system involved in the pathogenesis of CVD is represented by naive T lymphocytes and their differentiation into T helper (Th), namely the effector cells: Th1, Th17, and Th2. Each produces its own panel of cytokines mediating different functions, but Th1 and Th17 predominate in atherogenesis[4,5] (Fig. 1).

Monocyte chemoattractant protein-1 (MCP-1) or chemokine C–C ligand 2 (CCL2), the recent name of this chemotactic cytokine, is a member of the C–C chemokine family and a potent chemotactic factor for monocytes .[6] Due to its influence on many diseases and potential in the treatment of those diseases, MCP-1 is one of the most studied chemokines. MCP-1 is produced by endothelial, epithelial, smooth muscle, mesangial, microglial, and monocytic cells, fibroblasts, and astrocytes. In general, after receiving stimulus by inflammatory cytokines, chemokines are secreted to recruit cells like macrophages, lymphocytes, and neutrophils (Fig. 1).[6]

Once induced, chemokines bind to appropriately exposed receptors in immune cells through a chemical bond gradient. Compatible cells with such receptors can migrate from the site with high concentrations of chemokines to exert their functions: immune, homeostatic, or both. Inflammatory chemokines control the recruitment of leukocytes in inflammation and tissue injury, whereas homeostatic chemokines fulfill housekeeping functions, such as navigating leukocytes to secondary lymphoid, bone marrow, and thymus.

The CCR2 receptor is not exclusive to MCP-1, even though it is the major chemokine attractive monocytes receptor, and this binding is the most extensively studied in atherosclerosis and CVD. Indeed, this interaction between chemokines and their receptors is a challenging topic. Some studies have linked MCP-1 to CVD, either in animal models or in humans, predicting atherosclerosis complications.[7–10]

We reviewed the main observational studies that have analyzed serum MCP-1 in patients with hypertension regardless of CVD, relating them to target organ damage (TOD).

Methods

We conducted a structured review until June 2021 by searching the National Library of Medicine (NLM) PubMed, Index

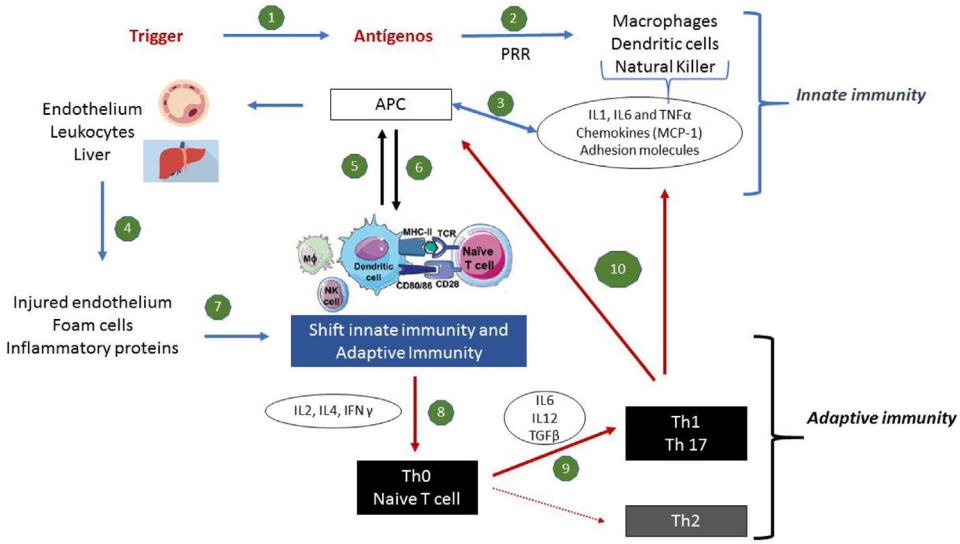

Figure 1 Schematic view of the action of inflammatory biomarkers. (1) The trigger may be an internal or external injury, notably an inflammation. (2) Macrophages, monocytes and dendritic cells (innate immunity cells) are activated by their ability to recognize foreign substances or endogenous antigens by pattern recognition receptors (PRR), releasing alarm's signals. (3) These first cells act as antigen presenting cells (APC) in a nonspecific inflammatory way, producing cytokines, chemokines (MCP-1), and expression of adhesion molecules that will act on the target cells. (4) These signs increase endothelial damage, and activation of leukocytes and hepatocytes. The injured endothelium is a major center of neoantigens driving this inflammatory wave since it promotes and hosts the activated monocytes, some of them filled with oxidized LDL (foam cells). (5) The innate immunity is stimulated by bringing new PRR. (6) The adaptive immunity previously stimulated, has no power to differentiate and propagate alone. (7) The stimulus for the secondary thymus and lymphoid organ also comes from endothelium, other inflammatory cells and hepatocytes. (8) The second feedback loop (not completely described), act differentiating and activating adaptive immunity cells through interleukins (IL2, IL4 and IFNγ) secreted by activated target cells. (9) The two main lymphocyte subtypes stimulated in atherosclerosis are Th1 and Th17 cells that ultimately close this second main cycle. (10) The production of IL-2 and IFNγ by Th1, and IL17 and IL6 by Th17, stimulate specially APC e.g., macrophages, foam cells, damaged endothelium and hepatocytes, closing a second inflammatory wave.

Medicus Latin-American (LILACS), and the Scientific Electronic Library Online (SciELO). The Mesh Terms ''Chemokine CCL2'' OR ''Monocyte Chemoattractant Protein-1'' AND ''Hypertension'', were included, returning 55 articles. Applying a filter for human studies and studies involving adults 19 years old or older, 33 and 30 articles remained, respectively. Two articles were not in English, leaving 28 for a detailed analysis.

There was a gradual growth in publications from the 1990s until 2005, reaching a peak between 2009 and 2013, with approximately 20 annual publications matching the search terms described above. In the past 5 years, fewer scientific articles have been published addressing this topic. We analyzed the biomarkers primarily in the representative sample of hypertension subjects (at least 30% of subjects), regardless of previous cardiovascular or cerebrovascular disease. Therefore, we analyzed 15 articles that comprised the criteria defined above.

The analysis of the articles was carried out by the following division:

Observational studies relating MCP-1 in patients with hypertension and free from cardiovascular disease, assessing the association with comorbidity, cardiovascular risk factors and target organ damage (Table 1).

Prognostic studies and MCP-1 relating with hypertension, CV risk factors, TOD, regardless of the presence of cardiovascular disease. We subdivided the studies by post hoc analysis, prospective analysis and meta-analysis (Table 2).

Results

Observational studies in patients free of cardiovascular disease (Table 1)

Regarding cardiovascular risk factors

There were a strong association between MCP-1 and older age, and male sex,[11,14] but divergent evidence on the relationship of MCP-1 with race and smoking was demonstrated in observational studies[13–16] (Table 1).

MCP-1 were analyzed in 2716 individuals without established CVD from a large American database.[16] The mean and median MCP-1 levels were significantly lower in African Americans than in whites, and this difference was retained after adjusting for age, gender, BMI, systolic blood pressure (SBP), diabetes, HDL and LDL cholesterol, triglycerides, physical activity index, smoking status, alcohol consumption, and hormone replacement. On the other hand, the African-PREDICT Study enrolled 403 healthy individuals whose men had higher MCP-1 values than women, and black race was associated with higher values of MCP-1 than whites.[18] The MCP-1 levels were lower than in other studies, possibly because this study enrolled young people without CVD.

There was strong association between MCP-1 and hypertension without confounding factors.[12,13,15,19] Madej et al. MCP-1 in plasma of 18 hypertensive patients and 18 healthy persons, excluding other CVD risk factors, such

Table 1 Observational studies assessing MCP-1 in subjects free of cardiovascular disease.

Study (year) Ref []	Patients enrolled (*n*)	Study details	MCP-1 levels	Parameters studied	Relation with MCP-1
Madej et al. (2005)[12]	18 HT vs 18 healthy	Hypertensive patients off treatment and without comorbidities.	Mean 142.2 vs 95.4 (HT vs healthy)	ICAM and MCP-1. Excluded other CVD risk factors.	Mean MCP1 levels higher in hypertensives
Antonelli et al. (2012)[15]	140 HT vs 140 without HT, but with other comorbidities.	Relationship between MCP-1 and HT through simple e multivariate regression.	Median: 391 (143–758) for HT vs 288 (121–364) without HT	High cholesterol levels and high median values of MCP-1	Multivariate linear regression revealed that only SBP and DBP were associated with MCP-1
Deo et al. (2004)[14]	3499 (2971 completed 3ª visit) in Dallas Heart Study	Multiethnic Population-based cohort. All subjects between the ages of 30 and 65 years Mean age: 44 ±10 years HT: 33%.	Median: 167.9; 25th, and 75th were 123.1 and 226.1, respectively.	Association to MCP-1 and CAC when adjusting for traditional CV risk, but not when included age.	Old age, white race, hypertension, hypercholesterolemia, diabetes, smoking, family history of premature CAD, high CRP levels
Tang et al. (2007)[16]	2246 whites and 470 African American in NHLBI Family Heart Study	Population-based cohort. Mean age: 55 years 39% and 75% of HT, whites and black during follow up.	Median: 180.2 in whites and 168.2 in African Mean: 189.1 and 174.3, in whites and blacks, respectively.	MCP-1 levels were statistically higher in whom there were some CAC evidence.	MCP-1 and CAC were positively associated only after controlling for age and gender, loosing significance in the multivariate analysis.
Kriel, Fourie and Schutte (2017)[18]	403 healthy individuals aged 20–30 years. The African-PREDICT Study	MCP-1, IL-6, TNFα and VCAM-1 were analyzed separately between sex and race. All participants are normotensive.	Mean black vs white for men, 190 vs 154; Mean black vs white for women, 169 vs 136.	Interaction with sex for the association of cfPWV and MCP-1. Interaction with ethnicity for the association of cIMT and MCP-1.	cIMT and MCP-1 associated with black women. No significant associations of cfPWV or cIMT with MCP-1 in any of the other groups.

Table 1 (*Continued*)

Study (year) Ref []	Patients enrolled (*n*)	Study details	MCP-1 levels	Parameters studied	Relation with MCP-1
Tan et al. (2014)[17]	116 patients free of cerebrovascular events or ACS.	Association MCP-1 with carotid atherosclerosis by US and cIMT Mean age: 64 ± 14.5 years	Quartiles were ≤32.4 (Q1), 32.5–62.5 (Q2), 62.6–106.4 (Q3), and ≥106.5 (Q4). MCP1 by the cIMT tertiles: 46, 80 and 86.	cIMT was significantly affected by HT and by MCP-1. HT 36% in the first tertile, 45% in the second and 80% in the last tertile.	MCP-1 independently associated with just the intima media thickness (cIMT), but not with plaque morphology.
Stumpf et al. (2016)[13]	39 with HT and 30 healthy controls	MCP-1 levels in HT vs healthy. No differences between groups regarding age, sex or BMI	Healthy: 144.5 vs HT: 252.8 (mean).	HT with MAU: 276.7 vs HT without MAU: 218.5.	Increased levels of MCP-1, with even higher levels in patients with RHTN and microalbuminuria.
Ritter et al. (2017)[19]	120 subjects with RHTN and 136 with HT. Mean age HT: 65 vs mean age RHTN: 60 ($p < 0.001$)	MCP-1 levels in patients with RHTN vs with mild to moderate hypertension and its association with LVH.	Median: 125 Mean MCP-1 with RHTN: 178 Mean MCP-1 with HT: 153 ($p = 0.47$).	Lower levels of MCP-1 (105) in patients with LVH vs without LVH (136).	No differences between groups. MCP- 1 above the median were independently associated with LVH logistic regression model.

Studies arranged in ascending order of publication. MCP-1 values are in pg/ml and age in years. Abbreviations: ACS, acute coronary syndrome; CAC, coronary artery calcification; CAD, coronary artery disease; CVD, cardiovascular disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HT, hypertension; cIMT, carotic intima-media thickness; IL-6, interleukin 6; ICAM, intercellular adhesion molecule; LVH, left ventricular hypertrophy; MAU, microalbuminuria; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; PWV, pulse wave velocity; RHTN resistant hypertension; SBP, systolic blood pressure; TNFα, tumor necrose factor alpha; US, ultrasonography.

Table 2 Prognostic studies regarding MCP-1.

Study (year) Ref []	Study details and patients enrolled	Parameters	Effects on MCP-1
De Lemos et al. (2003)[10]	Post Hoc *analysis* OPUS-TIMI 16 trial: evaluated MCP-1 in a follow up 10 months. 2270 with ACS compared to 279 healthy subjects.	Higher MCP1 in ACS (178 vs 157). Multivariate analysis: top quartile and 75% percentile of MCP-1 (>325 and >238, respectively) have increased risk of death or AMI.	Positive association: age, hypertension, diabetes, CAD, HF, CKD, female gender and BNP. No association: smoking, BMI, EF, troponin or CRP
Gregg, L.P (2018)[8]	Post Hoc *Analysis* Population-based, longitudinal cohort of 3257 participants, including 286 (8.8%) with CKD	MCP-1 with eGFR, albuminuria, death, and hard CV outcomes in CKD and non-CKD individuals.	MCP-1 increased with decreased GFR; it remained an independent risk factor for death in CKD. Modest but statistically significant association between MCP-1 and albuminuria in the entire cohort (non-significant when stratifying by CKD presence)
De Lemos et al. (2007)[9]	*Prospective Analysis* MCP-1 at 0, 4 and 12 months to correlate with CV outcomes comparing early and intensive statin therapy. Nearly 3000 reached the end of the study	MCP1 238: derived from a previous large study. After adjustment, CRP, BNP, MCP-1 >238 was independently associated with mortality, and fatal and non-fatal CV outcomes. No benefit of early and intensive statin therapy.	4^{th} month follow-up, the MCP-1 were independently associated with mortality. MCP-1 levels were not associated with baseline CRP or BNP levels. Modestly lower MCP-1 levels in the simvastatin 40 mg/80 mg arm at 4 months, but no differences at 12 months.
Ding et al. (2015)[7]	*Prospective Analysis* Enrolled 1980 Chinese patients, but 1411 with CAD were included. Follow up 3.3 years in mean	Serum MCP-1 levels were log-transformed and then classified into tertiles. MCP-1 showed non-linear associations with the outcomes.	Addition of MCP-1 to the fully adjusted model increased the predictive capacity for all-cause mortality and for CVD mortality.
Georgakis et al. (2019)[11]	*Meta-analysis* Six population-based prospective cohort studies with more than 17,000 stroke-free individuals. Mean follow-up time of 16 years.	Associations between baseline MCP-1 levels and incident fatal and non-fatal stroke. MCP-1 levels were included in the models adjusted for age, sex, and race, and additionally adjusted for conventional vascular risk factors	Higher circulating MCP-1 levels were associated to older age, male sex, higher systolic BP, T2DM, higher LDL and HDL cholesterol levels, higher BMI, current smoking, lower estimated GFR, history of CAD. Higher MCP-1 at baseline were at increased risk of ischemic stroke in both models.

MCP-1 values are in pg/ml. Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; CAC, coronary artery calcification; CRP, C-reactive protein; CKD, chronic kidney disease; CVD, cardiovascular diseases; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HT, hypertension; T2DM, type 2 diabetes mellitus; MCP-1, monocyte chemoattractant protein-1; MS, metabolic syndrome.

as hyperlipidemia, diabetes mellitus, obesity, and the presence of atherosclerotic plaques in carotid or vertebral arteries on doppler examination.[12] Plasma levels of both markers were significantly higher in newly diagnosed and off-treatment hypertensive patients compared to controls.

An Italian group observed the relationship of CCL2 (MCP-1) between 140 people with hypertension and 140 without hypertension.[15] The median values of MCP-1 were significantly higher in the hypertensive group. Multivariate linear regression controlling for the main factors, such as age, BMI, creatinine, cholesterol levels, triglycerides, and systolic BP and diastolic BP, revealed that only these last two parameters (SBP and DBP) were associated with MCP-1 levels, regardless of other covariates.

With a greater number of comorbidities, there is a tendency toward higher levels of MCP-1.[13,19] There were

regular associations of MCP-1 with a family history of coronary artery disease, hypercholesterolemia, diabetes and metabolic syndrome.[13–15]

Regarding target organ damage

Strong association. There were association with reduced glomerular filtration rate (GFR) and early stages of endothelial injury, such as albuminuria.[13] In patients with hypertension increased MCP-1 levels were showed, with even higher levels in patients with resistant hypertension and microalbuminuria.

Subclinical coronary artery disease by CAC was weak related to MCP-1 and showed a different behavior between whites and African descendent.[14,16]

Weak association. Coronary artery calcification (CAC) score and MCP-1 were analyzed in 2716 individuals without established CVD from a large American database.[16] MCP-1 was positively associated with CAC score after controlling for age and gender, but only in whites. Bivariate analysis was done by grouping CAC scores as those above zero (1466 subjects) and those with zero scores. There was no evidence of subclinical atherosclerosis in 1250 subjects, and MCP-1 levels were statistically higher in those with subclinical CAD by coronary computed tomography. In multivariate analysis adjusted for other CV risk factors, the relation between CAC and biomarkers was lost for both scores.[16] The association of CAC and MCP-1 has also been previously studied in 2004 in more than 3400 subjects without established CAD.[14] The researchers found a relationship between CAC score and MCP-1 after adjustment for traditional CV risk factors but did not include age, exactly opposite to Tang et al.,[16] who found only a relationship for sex and age when adjusting from multivariate analysis.

Trends or divergent results. There is a trend to relate carotid intimal media thickness (cIMT) to hypertension and MCP-1.[17,18] Pulse wave velocity (PWV) needs further studies and there were no association.[18]

Inconsistent data related to left ventricular hypertrophy (LVH).[19]

Carotid wall thickness by cIMT was positively and weakly associated with MCP-1 in black women but not in the other groups.[16] In a similar study, 116 patients free of cerebrovascular disease or CAD were analyzed by ultrasound for MCP-1 values and their relationship with cIMT and carotid atherosclerotic plaque morphology.[16] MCP-1 concentrations were independently associated with cIMT but not with plaque morphology. MCP-1 and two vascular parameters (arterial stiffness by PWV and cIMT[18] were studied in 403 healthy individuals. cIMT and MCP-1 associated with black women. No significant associations of cfPWV or cIMT with MCP-1 in any of the other groups. The Brazilian authors found no difference in MCP-1 levels between 120 subjects with resistant hypertension (RHTN) and 136 subjects with hypertension. Combining all subjects revealed lower levels of MCP-1 in patients with LVH compared to patients without LVH (105 versus 136, respectively). A logistic regression model adjusted for BMI, age, race, aldosterone levels, diabetes, RHTN, and the median MCP-1 (125 pg/ml) showed that MCP-1 levels above the median were independently associated with LVH in the entire population of hypertensive individuals.

Cardiovascular prognostic studies and MCP-1 (Table 2)

Post hoc analysis

The OPUS-TIMI 16 trial has analyzed the CV outcomes and overall mortality in a cohort of individuals with acute coronary syndrome (ACS) (2270 subjects) compared to 279 healthy subjects after having evaluated MCP-1 as the dependent variable.[10] Although the lower values were consistent with other studies, patients with ACS had MCP-1 values that were significantly higher than the controls (178 vs 157 pg/ml). Once again, high MCP-1 levels were positively related to advanced age, hypertension, diabetes, CAD, and heart failure. The novelty was the positive association to chronic kidney disease, female gender, and high BNP levels. In contrast, there was no association to smoking, body mass index (BMI), ejection fraction, troponin, or CRP. During follow-up of just 10 months, the authors realized that the top quartile and 75% percentile of MCP-1 (above 325 pg/ml and above 238 pg/ml, respectively) had increased risk of death or acute myocardial infarct (AMI) after adjusting for traditional risk factors.

In a large longitudinal cohort, Gregg et al. showed higher MCP-1 levels associated with lower eGFR and across higher CKD stages, but did not correlate with albuminuria in CKD patients.[8] They also had shown independently association with death after adjusting for traditional CV risk factors in both CKD and non-CKD individuals. The association between albuminuria and MCP-1 might not have been apparent because largely of individuals without CKD that had very little albuminuria.

Prospective analysis

Nearly 3000 subjects reached the end of study comparing CV outcomes about early and intensive statin therapy or delayed therapy (placebo for 4 months followed by simvastatin 20 mg/day through the end of the study).[9] After adjustment for major clinical predictors of CV risk, CRP and BNP MCP-1 above 238 pg/ml was independently associated with mortality and fatal and non-fatal CV outcomes. From the fourth month of follow-up, the MCP-1 levels were independently associated with mortality. Despite the direct relationship between MCP-1 and cholesterol, the work did not identify the benefit of early and intensive statin therapy over MCP-1 values.

MCP-1 was measured at baseline in 1411 CAD Chinese patients between 40 and 85 years old, and these patients were followed for an average of 3.3 years.[7] One-hundred-seventeen deaths were recorded, 88 of which were due to CVD. The multivariable-adjusted hazard ratios across tertiles of MCP-1 and the addition of serum MCP-1 to the fully adjusted model increased the predictive capacity for all-cause mortality and CVD mortality. Despite this, serum MCP-1 showed non-linear associations with the outcomes.

Meta-analysis

In a recent meta-analysis, six population-based prospective cohort studies were selected containing more than 17,000 stroke-free individuals with a mean follow-up time of 16 years.[11] The authors looked for associations between baseline MCP-1 levels and incident fatal and non-fatal stroke.

MCP-1 levels were included in the models adjusted for age, sex, and race, and adjusted for conventional vascular risk factors, including IL-6 and CRP levels. As we have already seen, higher circulating MCP-1 levels were associated with older age, male sex, higher systolic BP, presence of diabetes mellitus, higher LDL and HDL cholesterol levels, higher BMI, current smoking, lower estimated GFR, history of CAD, higher CRP, and IL-6 levels. Subjects with higher MCP-1 levels at baseline as a continuous variable were at increased risk of ischemic stroke in a model adjusted for age, sex, and race, and in the main model, further adjusted for vascular risk factors. Since there are no normal values, MCP-1 categorization in quartiles showed that the highest had a significantly higher risk than the lowest quartile.

Discussion

Regarding the consistent associations of MCP-1 among studies, three points warrant highlighting: the strong association of higher average MCP-1 levels in men and older people; the strong relationship with hypertension without confounding factors; and the divergence between chemokines and individual factors, such as race and smoking, should also be considered together with the use of potential anti-inflammatory effects of drugs.

The association of elevated levels of MCP-1 and hypertension, regardless of other confounding factors, has been well established.[12,15] In most cases, positive correlations were detected between MCP-1 levels and CV risk factors, including older age, white race, hypertension, hypercholesterolemia, diabetes, smoking, family history of premature CAD, reduced GFR, and high CRP levels.[13,14,16] The higher the MCP-1 levels, the higher the levels of other markers, or the greater prevalent of CV risk factors.

Regarding target organ damage and MCP-1, observational studies suggested early involvement, especially those with endothelial dysfunction. There was a strong association with reduced GFR and albuminuria.[11,13,14] Stumpf et al. compared MCP-1 levels between 39 patients with hypertension and 30 healthy controls, verifying these relations with TOD.[13] Those with hypertension showed significantly increased levels of MCP-1, with even higher levels in patients with hypertension and albuminuria, supporting the relationship of MCP-1 and TOD.

Besides that, there was no consensus about race, smoking, subclinical CAD, or PWV.[13,18] Subclinical CAD by CAC was related to MCP-1 but showed a different behavior between whites and those of African descendent.[14,16] The conclusions turned out to be similar in both studies: first, MCP-1 was not significantly associated with subclinical atherosclerosis after adjusting for established CVD factors when it includes the age in multivariate analysis; second, they agree on evidence of lower MCP-1 serum levels in those of African descent which do not necessarily have less subclinical atherosclerosis. This raised the hypothesis that MCP-1 and CAC behave differently among racial groups.

There was a trend to relate cIMT to hypertension and MCP-1.[17,18] Carotid wall thickness was positively associated with MCP-1 in black women but not in the other groups.[18] In another study, the higher the cIMT, the higher the MCP-1 levels and the hypertension prevalence.[17] Surprisingly, two other target organs were not associated with MCP-1: PWV and LVH.[14,18,19] Large artery stiffness by cfPWV was similar between the black and white groups, but it was only positively associated with age in the black population.[18]

There was no difference in the prevalence of LVH among MCP-1 quartiles in the Dallas Heart Study.[14] MCP-1 levels were compared in patients with RHTN versus patients with mild to moderate hypertension and its association with the presence of LVH in all individuals.[19] They support the possibility of LVH as a marker of the inflammatory process regardless of the severity of hypertension, but they found lower levels of MCP-1 in patients with LVH compared to patients without LVH. Patients with RHTN and with several subclinical TOD usually had even higher MCP-1 values.[15,19] For example, Antonelli et al. showed differences between groups: 391 pg/ml for hypertensive and 288 pg/ml without the high BP.[15] The group with hypertension had significant differences between cholesterol levels, and hence, this could have raised the mean values of MCP1 in this sample.

In theory, MCP-1 might not have such a prominent rise curve. MCP-1 is an early monocyte-attracting chemokine and, unless the process is constantly stimulated, its levels will tend to stabilize on a plateau. Indeed, this plateau would be higher in hypertension in late stages with established TOD than the healthy population or patients with mild to moderate hypertension. Conversely, almost all individuals with RHTN and comorbidities were being treated with drugs that potentially reduce inflammatory markers, namely ACE inhibitors or angiotensin receptor blockers (ARB) and statins.[20–24]

Prognostic studies allow for greater elucidation, but they must be analyzed with caution. There were some limitations in the first study of Deo et al.[10]: there were no measured lipid levels, no serial measurements of MCP-1, a small number of participants in the control group (10% approximately) and post hoc analysis was conducted in quartiles and percentiles. To solve some of these limitations, in a subsequent work done 4 years later, the researchers added a predictive value to MCP-1 in ACS.[9] MCP-1 was measured at the beginning and 4 months and 12 months later to correlate with CV outcomes.

Two findings in the prognostic studies suggest that higher MCP-1 levels reflect chronic rather than just acute pathophysiologic processes.[9,10] First, MCP-1 levels have changed little between baseline and 4 months. Second, MCP-1 is only slightly higher in patients with ACS than in normal control subjects.[9] Observational studies that have associated CAC and thickening of the carotid with MCP-1 also suggest the hypothesis of a marker of atherosclerosis and chronic inflammatory process.[14,16–18] The lack of linearity with CRP, an acute phase reagent, hints at the greater stability of MCP-1.

Prognostic studies also confirm the described associations with sex, age, accumulation of CV risk factors, and associations with TOD. Most of these studies did not analyze genetic polymorphisms but have recently found Mendelian randomization of higher stroke risk among individuals with a genetic predisposition to higher lifetime MCP-1 levels.[25]

The potential to reduce MCP-1 levels and hence decrease attraction and activation of monocytes and macrophages was postulated.[11,25] The modulation of MCP-1 (or CCL-2) and its receptor continues to be analyzed in experimental and

human models, with numerous evidences in reducing the size of the atherosclerotic plaque.[26–29]

Conclusion

Therefore, the longer and severe the hypertension, the higher the MCP-1 values are likely to be. MCP-1 seems to be linked earlier in the disease, reaching high levels with TOD acquired over time. MCP-1 might be useful as a prognostic marker, better and even earlier than CRP.

Several individual and environmental factors, such as morbidities, medications, diet, and smoking, can alter the values of biomarkers. In patients with higher BP levels and several comorbidities, we expect a greater number of drugs prescribed, with potential effects on reducing biomarkers. This should be balanced against the degree of acquired TOD.

Consent for publication

Authors allow publication in accordance with the rules established by the journal.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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