MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 1822-1827
DOI: 10.12659/MSM.911897

Received: 2018.07.03
Accepted: 2018.10.19
Published: 2019.03.10

Decreased Serum Monocyte Chemoattractant Protein-1 (MCP-1) Expression in Patients with Upper Gastrointestinal Bleeding

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

A 1 Guohui Xing
D 2 Lili Wang
C 3 Wei Li
FG 1 Yanling Xu
B 1 Xia Shi
EF 3 Guixing Xu
A 1 Jiajun Zhang

1 Department of Digestive Medicine, Rizhao Traditional Chinese Medicine Hospital, Rizhao, Shandong, P.R. China
2 Department of Infectious Diseases, Qingdao Central Hospital, Qingdao, Shandong, P.R. China
3 Department of General Surgery, Rizhao Traditional Chinese Medicine Hospital, Rizhao, Shandong, P.R. China

Corresponding Author: Jiajun Zhang, e-mail: jiajunzhangd5@163.com
Source of support: Departmental sources

Background: The aim of this study was to investigate the expression of monocyte chemoattractant protein-1 (MCP-1) and its correlation with the blood lipid level in upper gastrointestinal bleeding (UGIB).

Material/Methods: A total of 118 patients with UGIB were enrolled in this study. The relevant indicators for blood lipid levels were detected using a biochemical analyzer. MCP-1 levels in the serum of patients was determined through enzyme-linked immunosorbent assay (ELISA). Statistical Product and Service Solutions (SPSS) 17.0 software was used for the statistical analysis. Two-sample *t*-test was used for the intergroup comparison. The significant indicators were included in a multivariate logistic regression model to analyze the prognostic factors of UGIB. Pearson analysis was applied to the correlation analysis. $P<0.05$ suggested that the difference was statistically significant.

Results: MCP-1 expression levels in patients with UGIB were significantly lower than that in the control group and were even further reduced in patients with massive hemorrhage. The levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) in the serum of patients with UGIB were decreased compared with those in the control group and these indicators of the blood lipid level were decreased much more in patients with massive hemorrhage. The MCP-1 expression was positively correlated with the levels of TC, TG, and LDL in serum. MCP-1 and TC were the prognostic influencing factors of UGIB.

Conclusions: Serum MCP-1 expression was significantly decreased in patients with UGIB and correlated with blood lipid level, suggesting it might be a prognostic factor for UGB.

MeSH Keywords: Apolipoproteins • Cholesterol • Triglycerides

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/911897

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Upper gastrointestinal bleeding (UGIB) refers to hemorrhage in the digestive tract above the Treitz ligament, which is caused by lesions of the esophagus, stomach, duodenum, pancreas, or gallbladder. It is also the most fatal complication of esophagus, stomach, and duodenal diseases [1]. The incidence of UGIB is about 4 times as high as that of lower gastrointestinal bleeding, which is the primary cause of the death of gastrointestinal bleeding. According to statistics, the current incidence of UGIB is about 100 per 100 000 people per year with a mortality rate of 6–10% [2]. Endoscopic hemostasis, application of proton pump inhibitor (PPI), blood transfusion, and the correction of coagulation disorders are the main treatments for UGIB. In addition, adequate fluid resuscitation is required to prevent circulatory failure. However, the gastrointestinal bleeding and the large amount of liquid infusion in follow-up treatment can easily lead to abnormal metabolism such as anemia, water-electrolyte imbalance, and dyslipidemia [3]. There is no available literature that evaluates the correlations of UGIB with dyslipidemia.

Dyslipidemia mainly includes abnormalities in total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and apolipoprotein (Apo). Dyslipidemia plays important roles in the occurrence and development of cardiovascular diseases. A previous study demonstrated that hyper-LDL cholesterolemia, hypo-HDL cholesterolemia, and hypercholesterolemia were closely associated with primary intracerebral hemorrhage [4]. In addition, patients with rebleeding have been shown to more frequently be older, more often have a history of previous transient ischemic attack or ischemic stroke, and less often have hyperlipidemia than patients without rebleeding [5]. However, the effects of blood lipid upon the prognosis of UGIB remains poorly understood.

Monocyte chemoattractant protein-1 (MCP-1), also known as chemokine (C-C motif) ligand 2 (CCL2), is mainly expressed in inflammatory cells and endothelial cells. MCP-1 expression is upregulated after pro-inflammatory stimulation and tissue damage, and is associated with atherosclerotic lesions [6–8]. Atherosclerosis is a cumulative disease that begins with the aggregation of lipids, lipoproteins, and immune cells on the artery walls. It has been reported that MCP-1 plays an important role in the pathogenesis of atherosclerosis, and there is abundant evidence indicating that monocytes containing MCPs and macrophages can affect the growth of other types of cells in atherosclerotic lesions. Previous studies have suggested that elevated MCP-1 expression is associated with hypercholesterolemia and hypertriglyceridemia [9,10]. At present, there are few studies on the role of MCP-1 in UGIB. In this study, the effects of MCP-1 on UGIB were investigated in patients with UGIB.

Material and Methods

Patients

This study included 118 patients with UGIB who were admitted to the Gastroenterology Department of our hospital. The inclusion criteria were as follows: 1) patients who were over 18 years of age, 2) patients whose diagnosis was confirmed through endoscopic examination, and 3) patients with UGIB symptoms such as hematemesis or melena, and some patients had clinical manifestations of hemorrhagic shock. Exclusion criteria were as follows: 1) pregnant and lactating women with abnormal levels of lipoprotein and cholesterol metabolism, 2) patients with severe cardiovascular and cerebrovascular diseases with high HDL cholesterol levels, 3) patients with severe liver or kidney dysfunctions or thyroid dysfunctions with abnormal lipid metabolism, and 4) patients who took lipid-lowering drugs within 1 month, with lower lipid levels. The study protocol was approved by the Research Ethics Committee of our hospital, and all patients gave their informed consent before study commencement. This study was performed in agreement with Helsinki declaration.

In addition, there were 45 normal patients, who received physical examinations during the same study period, who were enrolled as the control group for this study (Table 1).

Determination of blood lipid

All the included patients and those in the normal control group were admitted to the Gastroenterology Department of our hospital. We collected 5 mL of fasting venous blood from patients in the early morning on the second day of admission. The blood samples were placed into a blood collection tube which contained separation gel to obtain serum samples. Then the Hitachi full automatic biochemical analyzer in our hospital was used to detect the blood lipid-related indicators such as TC, TG, HDL, LDL, ApoA, and ApoB.

Detection of serum MCP-1 level in patients through enzyme-linked immunosorbent assay (ELISA)

Then 4 mL samples of fasting whole blood drawn from patients and controls were placed at room temperature for 1 hour. The serum was obtained by centrifugation at 1000 g. The dilution (1: 50) was performed in a small test tube provided in the kit according to the corresponding standard protocol. The reagent was mixed uniformly during dilution. Foaming was avoided as much as possible during the operation process and the serum samples were not diluted after centrifugation. Bromodeoxyuridine-enzyme-linked immunosorbent assay (BrdU-ELISA) kit was bought from Roche, Switzerland. The MCP-1 level in serum samples was detected in strict accordance with the kit manual. This experiment was repeated 3 times to obtain an average value.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Basic data of experimental group and control group.

		Gender	
		Male (n)	Female (n)
UGIB group	Peptic ulcer	33	30
	Acute gastric mucosal lesion	7	8
	Liver cirrhosis variceal hemorrhage	8	10
	Gastrointestinal tumor hemorrhage	11	9
	Vascular malformation	2	0
Control group		22	23

Statistical analysis

Statistical Product and Service Solutions (SPSS) 17.0 software was used for statistical analysis. The measurement data were expressed as mean ± standard deviation (SD). Student *t*-test was used for the intergroup comparison. Univariate logistic regression analysis was applied. The significant indicators ($P<0.05$) were included into the multivariate logistic regression model to analyze the prognostic factors of UGIB. Pearson analysis was applied to the correlation analysis. $P<0.05$ suggested that the difference was statistically significant.

Results

MCP-1 expression in the UGIB group and the normal control group

The level of MCP-1 in the serum of the experimental group and the control group were detected by ELISA. The results showed that the expression level of MCP-1 in patients with UGIB was significantly lower than that in the normal control group ($P<0.05$, Figure 1).

Blood lipid level in the UGIB group and the normal control group

The results of biochemical analysis of the blood lipid indicators showed that TC in the UGIB group (1.07±1.19 mmol/L) was significantly decreased compared with that in the control group (1.63±1.01 mmol/L) ($P=0.031$). TG in the UGIB group (3.21±1.02 mmol/L) was also significantly lower than that in the normal control group (4.93±1.08 mmol/L) ($P = 0.002$), together with significantly reduced LDL level in the UGIB group (1.89±0.72 mmol/L) than that in the normal control group (2.81±0.79 mmol/L) ($P=0.011$). However, there were no significant differences in the levels of ApoA, ApoB, and HDL between the 2 groups ($P>0.05$, Table 2).

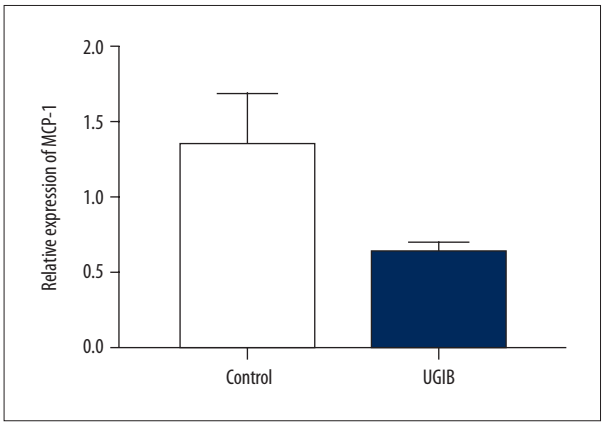

Figure 1. MCP-1 expression levels in the normal group and the upper gastrointestinal bleeding group.

Correlations of MCP-1 expression level with UGIB hemorrhage amount

According to the amount of hemorrhage, patients were divided into a massive hemorrhage group (group A, n=42) and a moderate hemorrhage group (group B, n=76). The expression level of MCP-1 in the massive hemorrhage group, the moderate hemorrhage group, and the control group were compared. It was shown that the level of MCP-1 expression in the massive hemorrhage group was significantly lower than that in the moderate hemorrhage group ($P<0.05$, Figure 2).

Correlations of the blood lipid level with UGIB hemorrhage amount

The results of biochemical analysis of the blood liquid indicators in the massive hemorrhage group and the moderate hemorrhage group showed that in the massive hemorrhage group, TC (1.01±0.89 mmol/L) was significantly lower than that in the moderate hemorrhage group (1.47±0.19 mmol/L) ($P=0.042$). Consistently, TG (2.21±1.12 mmol/L) was also significantly reduced compared with the moderate hemorrhage group (3.51±1.06 mmol/L) ($P=0.012$), with significantly lower

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. The levels of detection indicators in the UGIB group and control group.

Detection indicators	Experimental group (n=118)	Control group (n=45)	*p*
TC (mmoL/L)	1.07±1.19	1.63±1.01	0.031
TG (mmoL/L)	3.21±1.02	4.93±1.08	0.002
HDL (mmoL/L)	1.16±0.17	1.21±0.22	0.076
LDL (mmoL/L)	1.89±0.72	2.81±0.79	0.011
ApoA (mmoL/L)	1.34±0.21	1.73±0.31	0.061
ApoB (mmoL/L)	0.82±0.26	1.24±0.39	0.054

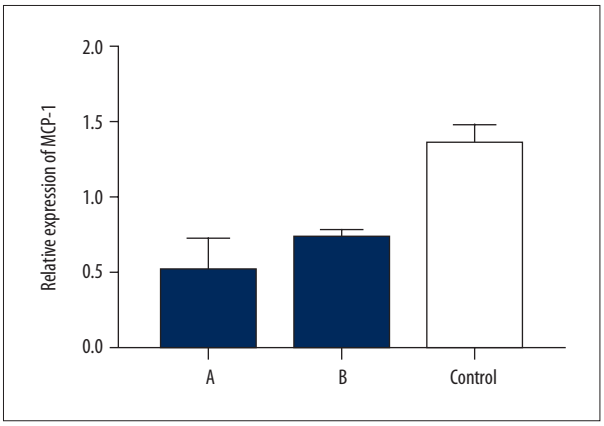

Figure 2. Correlations of MCP-1 level with the upper gastrointestinal bleeding amount.

Table 4. Results of univariate correlation analysis of MCP-1 in patients with UGIB.

Clinical indicators	Correlation analysis	
	r	p
TC (mmoL/L)	0.113	0.318
TG (mmoL/L)	0.581	0.002
HDL (mmoL/L)	–0.241	0.212
LDL (mmoL/L)	0.667	0.023
ApoA (mmoL/L)	0.583	0.656
ApoB (mmoL/L)	0.665	0.432

LDL (1.59±0.74 mmol/L) compared with the moderate hemorrhage group (1.99±0.62 mmol/L) (P=0.031). However, there were no significant differences in ApoA, ApoB, and HDL between the 2 groups (P>0.05) (Table 3).

Correlations of MCP-1 expression with the blood lipid level

The correlations of MCP-1 expression with the relevant indicators of blood lipid level were determined by univariate analysis and revealed that MCP-1 expression was positively correlated with the levels of TC and LDL (P<0.05, Table 4).

Univariate logistic regression analysis

Taking the occurrence of gastrointestinal bleeding as a dependent variable, non-conditional logistic regression analysis was performed to analyze the correlations of the gastrointestinal bleeding risk with the related variables such as *P*,

Table 3. Blood lipid indicators in the massive hemorrhage group and the moderate hemorrhage group.

Detection indicators	Massive hemorrhage group (n=42)	Moderate hemorrhage group (n=76)	Control group (n=45)	*p*
TC (mmoL/L)	1.01±0.89	1.47±0.19	1.63±1.01	0.042
TG (mmoL/L)	2.21±1.12	3.51±1.06	4.93±1.08	0.012
HDL (mmoL/L)	1.26±0.17	1.16±0.17	1.21±0.22	0.079
LDL (mmoL/L)	1.59±0.74	1.99±0.62	2.81±0.79	0.031
ApoA (mmoL/L)	1.31±0.23	1.24±0.21	1.73±0.31	0.071
ApoB (mmoL/L)	0.89±0.28	0.92±0.26	1.24±0.39	0.064

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 5. Results of univariate logistic regression analysis of UGIB.

Factor	Regression coefficient	Standard error	Wald	*p*	OR (95% CI)	
Gender	–0.59	0.196	0.063	0.092	0.962	(0.639–1.397)
Age	0.115	0.026	0.537	0.879	0.852	(0.639–1.798)
TG	–2.131	0.088	61.340	0.042	1.298	(0.784–1.361)
TC	–1.131	0.125	79.780	0.032	0.997	(0.675–1.131)
HDL	–3.677	0.412	80.035	0.721	0.587	(0.443–1.112)
LDL	–1.223	0.147	71.319	0.003	0.978	(0.678–1.231)
ApoA	–2.983	0.366	66.272	0.234	0.667	(0.329–0.975)
ApoB	–2.866	0.418	47.705	0.452	0.742	(0.563–0.876)
MCP-1	–2.022	0.008	47.370	0.001	1.311	(0.873–1.219)

Table 6. Results of the multivariate logistic regression analysis of UGIB.

Factor	Regression coefficient	Standard error	Wald	*p*	OR (95% CI)	
TG	–0.631	0.088	61.340	0.072	1.098	(0.741–1.261)
TC	–1.331	0.135	79.780	0.022	0.947	(0.625–1.141)
LDL	–0.923	0.157	71.319	0.083	0.778	(0.679–1.131)
MCP-1	–2.322	0.018	435.370	0.011	1.411	(0.973–1.519)

odds ratio (OR), and 95% confidence interval (95% CI). Significant indicators were screened by univariate logistic regression analysis ($P<0.1$) and the following indicators were included in the multivariate regression analysis model: TG ($P<0.05$, OR=1.298, 95% CI=0.784–1.361), TC ($P<0.05$, OR=0.997, 95% CI=0.675–1.131), LDL ($P<0.01$, OR=0.978, 95% CI=0.678–1.231), and MCP-1 ($P<0.001$, OR=1.311, 95% CI=0.873–1.219) (Table 5).

Multivariate logistic regression analysis

Results of the multivariate logistic regression analysis of the aforementioned indicators showed that UGIB was significantly associated with TC ($P=0.022$, OR=0.947, 95% CI=0.625–1.141) and MCP-1 ($P=0.011$, OR=1.411, 95% CI=0.973–1.519) (Table 6).

Discussion

Dyslipidemia is not only involved in the occurrence and development of cardiovascular diseases, but also closely related to the occurrence and prognosis of malignant tumors such as breast cancer and lung cancer [11,12]. In recent years, there have been more and more studies on the correlation of dyslipidemia with hemorrhage, among which the most frequent study topic has been the effects of dyslipidemia on intracerebral hemorrhage. However, with the continuous deepening of research, it has been found that dyslipidemia also exists in the context of gastrointestinal bleeding. The results of the present study found that the level of blood lipids in the gastrointestinal bleeding group was significantly lower than that in the normal control group. Moreover, the level of blood lipids was much lower in the massive hemorrhage group, suggesting that dyslipidemia may play a role in the occurrence and development of the gastrointestinal bleeding. However, the exact molecular mechanism by how dyslipidemia is involved in the pathogenesis of gastrointestinal bleeding remains to be further elucidated. The possible reason might be that under the stress response of gastrointestinal bleeding, a series of changes occur in the body, leading to abnormal lipid metabolism. At the same time, in the case of abnormal lipid metabolism, the secretion of corresponding cytokine is reduced, and vascular endothelial cells are damaged, resulting in gastrointestinal bleeding. Nevertheless, how the pathological processes of dyslipidemia and gastrointestinal bleeding affect one another still needs further study.

MCP-1 is produced by macrophages and endothelial cells through activating the nuclear transcription factor-b

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

pathway [13]. During the inflammatory response, MCP-1 can recruit monocytes, leukocytes, and other inflammatory cells [14]. Circulating MCP-1 expression has been found to be elevated in a diet-induced obese mouse model [15,16], and it has been demonstrated in animal experiments that chemokine receptor 2 (CCR2), a MCP-1 receptor, exists on the adipocyte surface. Expression of MCP-1 messenger ribonucleic acid (mRNA) in adipose tissues, MCP-1 concentration in blood circulation, and body mass index (BMI) are closely related [17,18]. Bruun et al. [19] found that MCP-1 level released by the human visceral adipose tissues is higher than that of subcutaneous adipose tissues. MCP-1 promotes the infiltration of monocyte/macrophage into adipose tissues [20]. These findings suggest that MCP-1 expression is closely correlated with adipose metabolism. In our study, it was revealed that in patients with UGIB, the expression of MCP was positively correlated with the levels of TC and LDL, which is consistent with the previous findings. At the same time, we found that MCP-1 had a certain correlation with UGIB prognosis. The lower the level of MCP-1, the greater risk of gastrointestinal bleeding, as well as the worse prognosis of patients.

Conclusions

MCP-1 expression was decreased in patients with UGIB, suggesting it might be associated with the occurrence and development of UGIB, and suggesting manipulation of its expression might be beneficial for the treatment of UGIB. However, due to the limited number of patients and controls enrolled in the present study, larger cohort clinical studies are required to confirm these findings in the future.

Conflict of interest

None.

References:

1. Peixoto A, Goncalves R, Macedo G: Acute gastrointestinal bleeding caused by Dieulafoy lesion of the esophagus. Acta Med Port, 2017; 30(5): 426
2. Dertinger SH, Vestner H, Muller K et al: [Prospective study of diagnosis, therapy and follow-up of acute gastrointestinal hemorrhage in 397 patients]. Wien Klin Wochenschr. 1996; 108(22): 717–21 [in German]
3. Miilunpohja S, Karkkainen J, Hartikainen J et al: Need of emergency surgery in elderly patients with upper gastrointestinal bleeding: survival analysis during 2009–2015. Dig Surg, 2018 [Epub ahead of print]
4. Lucic PA, Cuzdi A, Zivanovic Z et al: Dyslipidemia as a risk factor for primary intracerebral hemorrhage. Med Glas (Zenica), 2014; 11(1): 31–36
5. Passero S, Burgalassi L, D'Andrea P et al: Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke, 1995; 26(7): 1189–92
6. Tabata T, Mine S, Kawahara C et al: Monocyte chemoattractant protein-1 induces scavenger receptor expression and monocyte differentiation into foam cells. Biochem Biophys Res Commun, 2003; 305(2): 380–85
7. Namiki M, Kawashima S, Yamashita T et al: Local overexpression of monocyte chemoattractant protein-1 at vessel wall induces infiltration of macrophages and formation of atherosclerotic lesion: Synergism with hypercholesterolemia. Arterioscler Thromb Vasc Biol, 2002; 22(1): 115–20
8. Rutledge BJ, Rayburn H, Rosenberg R et al: High level monocyte chemoattractant protein-1 expression in transgenic mice increases their susceptibility to intracellular pathogens. J Immunol, 1995; 155(10): 4838–43
9. Parissis JT, Venetsanou KF, Kalantzi MV et al: Serum profiles of granulocyte-macrophage colony-stimulating factor and C-C chemokines in hypertensive patients with or without significant hyperlipidemia. Am J Cardiol, 2000; 85(6): 777–9, A9
10. Garlichs CD, John S, Schmeisser A et al: Upregulation of CD40 and CD40 ligand (CD154) in patients with moderate hypercholesterolemia. Circulation, 2001; 104(20): 2395–400
11. Hudgins LC, Parker TS, Levine DM et al: A single intravenous dose of endotoxin rapidly alters serum lipoproteins and lipid transfer proteins in normal volunteers. J Lipid Res, 2003; 44(8): 1489–98
12. Kucharska-Newton AM, Rosamond WD, Schroeder JC et al: HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer, 2008; 61(3): 292–300
13. Gunn MD, Nelken NA, Liao X et al: Monocyte chemoattractant protein-1 is sufficient for the chemotaxis of monocytes and lymphocytes in transgenic mice but requires an additional stimulus for inflammatory activation. J Immunol, 1997; 158(1): 376–83
14. Lu B, Rutledge BJ, Gu L et al: Abnormalities in monocyte recruitment and cytokine expression in monocyte chemoattractant protein 1-deficient mice. J Exp Med, 1998; 187(4): 601–8
15. Sartipy P, Loskutoff DJ: Monocyte chemoattractant protein 1 in obesity and insulin resistance. Proc Natl Acad Sci USA, 2003; 100(12): 7265–70
16. Takahashi K, Mizuarai S, Araki H et al: Adiposity elevates plasma MCP-1 levels leading to the increased CD11b-positive monocytes in mice. J Biol Chem, 2003; 278(47): 46654–60
17. Christiansen T, Richelsen B, Bruun JM: Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associated with adiposity and reduced after weight loss in morbid obese subjects. Int J Obes (Lond), 2005; 29(1): 146–50
18. Salcedo R, Ponce ML, Young HA et al: Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood, 2000; 96(1): 34–40
19. Bruun JM, Lihn AS, Pedersen SB et al: Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): Implication of macrophages resident in the AT. J Clin Endocrinol Metab, 2005; 90(4): 2282–89
20. Stork S, Baumann K, von Schacky C et al: The effect of 17 beta-estradiol on MCP-1 serum levels in postmenopausal women. Cardiovasc Res, 2002; 53(3): 642–49

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]