CLINICAL STUDY

Monocyte chemoattractant protein 1: a possible link between visceral adipose tissue-associated inflammation and subclinical echocardiographic abnormalities in uncomplicated obesity

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Abstract

Objective: Obesity can be considered a state of chronic, low-grade inflammation. Particularly, visceral adipose tissue (VAT) seems to be an active compartment in pro-inflammatory molecule secretion. Adipocytes and VAT are able to produce large amounts of monocyte chemoattractant protein 1 (MCP-1), a chemokine directly involved in ventricular remodeling.

Design: In this study, the possible existence of a correlation between MCP-1, abdominal fat accumulation and echocardiographic abnormalities in uncomplicated obesity was investigated.

Methods: Echocardiographic parameters, MCP-1 and C-reactive protein (CRP) levels were assessed in 27 normotensive obese women of fertile age (body mass index 43.5 ± 4.8 kg/m², mean $\pm$ S.D.) and 15 normal weight women. Visceral fat (VAT) in the obese group was assessed by computed tomography. **Results:** Obese patients had higher MCP-1 ($P < 0.0001$) and CRP ($P < 0.0001$) levels than controls. MCP-1 levels were correlated with VAT area ($r = 0.57$, $P < 0.0001$), CRP ($P < 0.0001$), left ventricular mass (LVM) ($P < 0.02$), LVM indexed for height ($P < 0.03$), end-diastolic posterior wall ($P < 0.005$), relative wall thickness ($P < 0.01$), early diastolic filling wave velocity ($P < 0.01$), isovolumetric relaxation time ($P < 0.001$) and deceleration time ($P < 0.01$). Obese patients with greater amounts of VAT (> 130 cm²) presented higher MCP-1 ($P < 0.0001$) and CRP levels ($P < 0.04$) than those with a lower degree of abdominal adiposity.

Conclusions: MCP-1 levels and visceral adipose tissue seem to be associated with some morphological and functional echocardiographic abnormalities and support a role for visceral fat in predisposing the subject to cardiac dysfunction, possibly through a low-grade state of inflammation.

European Journal of Endocrinology 153 871–877

Introduction

Adipose tissue is far from being considered a simple fat-storage depot. Several studies demonstrate that it should be given the title of endocrine organ, able to produce and release a great variety of cytokines and hormone-like proteins such as tumor necrosis factor- α , interleukin-6, monocyte chemoattractant protein 1 (MCP-1) and the newly isolated protein, visfatin (1–4). Most of these mediators exert a systemic action as inflammatory pathway activators. In particular, MCP-1 has been implicated in the pathogenesis of several cardiovascular disorders such as chronic heart failure and myocarditis (5, 6). In fact, MCP-1 can directly affect cardiomyocytes and this observation introduces this chemokine as a potential enhancer of inflammatory responses within the myocardium (7). Elevated myocardial MCP-1 levels may play an important role in the pathogenesis of ventricular remodeling after myocardial infarction by inducing myocyte hypertrophy and

interstitial fibrosis (8). MCP-1 is a monomeric polypeptide belonging to the chemokine family that plays a crucial role in monocyte recruitment (9).

Adipose tissue macrophage infiltration has been demonstrated to increase proportionally in relation to adiposity (10) and to participate in inflammatory pathways that are activated in this body compartment in the obese state (10, 11).

Bruun *et al.* have recently demonstrated that MCP-1 release is higher in visceral adipose tissue (VAT) compared with subcutaneous adipose tissue (SAT), suggesting the former as a major source of the increased levels of MCP-1 (12).

Given that human adipose tissue is also metabolically active and able to secrete MCP-1 (13), it has recently been reported that reduction in visceral fat is directly correlated to a decrease in MCP-1 levels (14), supporting a role for VAT in the systemic inflammatory condition. At present, to our knowledge, literature about the correlation between MCP-1 and abdominal

adiposity is still scarce and poor evidence has been provided about a correlation between MCP-1 secretion and the VAT entity in humans (12).

It has been shown that intra-abdominal fat is correlated with subclinical cardiac alterations (15) and reduction of abdominal adiposity reduces the secretion of cytokines and improves cardiac function (16).

With this background it has been supposed that increased MCP-1 secretion, possibly by the visceral tissue, might influence cardiac morphology and function. Therefore, the aim of this study was to evaluate the possible existence of a correlation between MCP-1 and echocardiographic abnormalities by assessing their relation with VAT in uncomplicated obese women.

Subjects and methods

The study was performed according to the recommendations of the Declaration of Helsinki and all the subjects recruited gave informed consent to the examination protocol.

Subjects

Twenty-seven obese female patients of fertile age (mean age 33.3 ± 8.3 years (range, 21 to 50 years), mean body mass index (BMI) $43.5 \pm 4.8 \text{ kg/m}^2$ (range, $36.7\text{--}54.6 \text{ kg/m}^2$)) were recruited and underwent physical examination. None of the patients had a past history of heart, hepatic, renal, pulmonary, endocrine or neoplastic disease. They were all non-smokers (non-smoking habit for at least five years). No chronic inflammatory disease nor minor infection was detectable at the time of the study. None of the subjects was treated with drugs that could interfere with the study (statins, fibrates, thiazolidinediones, steroids, hormone replacement or nonsteroidal anti-inflammatory drugs). The patients were compared with 15 healthy normotensive and normal weight control women matched for age and height (mean age 36.8 ± 8.2 years (range, 23 to 49 years); mean BMI $22.6 \pm 1.7 \text{ kg/m}^2$).

Anthropometric measurement and VAT assessment

All the subjects were measured for height, weight, waist circumference, hip circumference, and BMI and waist/hip ratio (WHR) were calculated. Fat mass and fat-free mass were estimated by bioelectrical impedance analysis (BIA 101-S; Akern, Florence, Italy).

Adipose tissue accumulation in the obese group was assessed by computed tomography at the L4-L5 level. VAT and SAT areas were measured using a single scan at the L4 level and computed with attenuation values of between -150 and -50 Hounsfield units. The VAT/SAT area ratio was calculated. Abdominal

sagittal diameter in centimeters at the L4 level was also measured.

Echocardiographic measurements

The echocardiographic variables were collected using an M-mode color-doppler VSF (Vingmed-System Five; General Electric, Horten, Norway) with a 2.5- to 3.5-MHz transducer probe by the same experienced physician. Recordings were made on the left lateral decubitus position after 10 min supine rest. M-mode tracings were obtained from the parasternal left ventricular short-axis view and at a paper speed of 50 mm/s, and recordings were read by two different examiners blind to the biochemical data. End systolic and diastolic left ventricular volume (LVEDV), diameter (LVEDD), septum and posterior wall (PW) thickness and end systolic left atrium were measured according to the methods of the American Society of Echocardiography (17). Left ventricular mass (LVM) was calculated using the Penn convention (18) and normalized for height (in meters) to the 2.7 power ($\text{LVMh}^{2.7}$) to take into account the independent effect of obesity on left ventricle (LV) geometry (19). The relative wall thickness (RWT) was calculated as $2 \times \text{posterior wall/LV end-diastolic diameter}$ (2PW/LVEDD). LV diastolic function correlates (early (E) and atrial (A) diastolic filling wave velocities, E/A ratio, isovolumetric relaxation time (IVRT)) were evaluated using pulse-wave Doppler echocardiography.

Blood samples

Blood samples were drawn after overnight fasting for serum glucose, insulin (immunoradiometric assay), total cholesterol, high density lipoprotein cholesterol and triglycerides. Low density lipoprotein values were obtained according to the Friedewald formula. Insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and QUICKI (20). Serum samples were stored at -20°C and then assayed for C-reactive protein (CRP) levels by immunoturbidimetric assay (Roche-Hitachi Mannheim, Germany). Plasma MCP-1 concentrations were evaluated using a Quantikine Enzyme-Linked Immunosorbent Assay (ELISA) kit (R&D Systems, Abingdon, UK/ Inc., Minneapolis, MA, USA). According to the manufacturer's recommendations, 100 μl assay diluent (buffered protein base) and 100 μl sample or standard were added to each well of a polystyrene microplate coated with a monoclonal murine antibody against MCP-1. Each sample, standard and blank was assayed in duplicate. After incubating at room temperature for 2 h and washing with a buffered surfactant solution, 200 μl polyclonal antibody against MCP-1 conjugated with horseradish peroxidase were added to each well, incubated and washed again. Then 200 μl substrate solution (hydrogen peroxide and tetramethylbenzidine

as chromogen) were added to each well and incubated at room temperature for 20 min protected from light. Finally, 50 µl stop solution (2 M sulfuric acid) were added to each well and the absorbance was determined within 30 min using a microplate reader (EL-800, Bio-TEK Instruments, Inc., Winooski, VT, USA) set to 450 nm. The minimum detectable dose was determined to be 5 pg/ml.

Statistical analysis

Data are presented as means ± standard deviation (S.D.). Comparisons between the groups were analyzed using Student's two-tailed *t*-test. An unweighted linear regression model was used to evaluate the relationship between variables and stepwise regression analysis was used to assess the association between the MCP-1 values and indices of fat distribution. The relationship between MCP-1 and echocardiographic parameters was also evaluated after correction for VAT and CRP by a partial correlation method. All statistical analyses were performed by STATISTIX 4.1 (Analytical Software, Tallahassee, FL, USA). The significance level was established at $P < 0.05$.

Results

MCP-1, CRP and clinical-anthropometric variables

Anthropometric and clinical characteristics are summarized in Table 1. All fasting blood biochemical data from the obese group were within the normal range. According to the American Diabetes Association criteria (21) all the patients had normal glucose tolerance.

Plasma MCP-1 and CRP levels were significantly higher in obese women than in lean controls (71.9 ± 30.6 vs 41.7 ± 8.6 pg/ml, $P < 0.0001$ and 1.04 ± 0.6 vs 0.03 ± 0.03 mg/dl, $P < 0.0001$ respectively) (Fig. 1). In the obese group, a positive correlation between MCP-1 values and VAT ($r^2 = 0.57$,

$P < 0.0001$) (Fig. 2), VAT/SAT area ($r^2 = 0.67$, $P < 0.0001$) and CRP levels ($r^2 = 0.48$, $P < 0.0001$) was observed. No correlation of MCP-1 with SAT, BMI, waist circumference, WHR, fat mass and fat-free mass was found. In order to emphasize the role of fat distribution, multiple stepwise regression analysis (Table 2) was used to investigate the correlations of relative indices with MCP-1 and CRP levels. Plasma MCP-1 most closely correlated with VAT/SAT ($r^2 = 0.67$, $P < 0.0001$), whereas CRP was associated with VAT ($r^2 = 0.34$, $P < 0.002$); the other indices of fat distribution did not enter the model. It is noteworthy that, when separating the obese patients on the basis of VAT area (i. e. >130 cm² ($n = 15$) or <130 cm² ($n = 12$)) (22), higher MCP-1 (87.9 ± 32.7 vs 32.7 ± 8.7 pg/ml, $P < 0.0001$) and CRP levels (1.38 ± 0.55 vs 0.61 ± 0.32 mg/dl, $P < 0.04$) were observed in patients with higher abdominal adiposity.

MCP-1 and echocardiographic parameters

As recently reported in a similar series (15), obese patients showed an impairment of several echocardiographic parameters compared with lean subjects, and a significant correlation was detected between VAT area and some of the parameters. In the present study, MCP-1 levels were positively correlated with PW ($P < 0.005$) (Fig. 3A), LVM ($P < 0.02$) (Fig. 3B), LVMh^{2.7} ($P < 0.03$), RWT ($P < 0.01$), E ($P < 0.01$), IVRT ($P < 0.001$) (Fig. 3C) and deceleration time (DT) ($P < 0.01$) and CRP levels were also positively correlated with IVRT ($P < 0.003$). No correlation of MCP-1 and CRP was found with the other echocardiographic parameters. Even after correcting for increased values of VAT and CRP, a significant relationship ($P < 0.05$) between MCP-1 and some echocardiographic correlates (PW, IVRT and LVMh^{2.7}) was still detected (Table 3). Moreover, PW, RWT, IVRT and DT were also higher in patients with the greatest amount of VAT.

Discussion

It seems likely that VAT may represent an endocrine organ of linkage between obesity and inflammatory pathways (23) and that adipocytes are important synthesizers of bioactive proteins (1–4). Adipocytes are now known to be capable of expressing MCP-1 in the presence of serum or specific stimuli such as CRP (24, 25). In particular, the abdominal fat depot is a potent stimulator of CRP production by the liver and our results confirm the association between this inflammation index and VAT area (26). Epidemiological studies have shown that CRP is a strong predictor of coronary heart disease events (27) and a component of the atherothrombotic profile of abdominal obesity (26). Furthermore, patients with high CRP levels may be at risk of LV dysfunction and remodeling (28).

Table 1 Clinical and anthropometric characteristics of the study population. Data are expressed as means ± S.D.

Variable	Controls (<i>n</i> = 15)	Obese (<i>n</i> = 27)	<i>P</i>
Age (years)	36.8 ± 8.2	33.3 ± 8.3	ns
Weight (kg)	57.9 ± 7.4	107.6 ± 12.0	<0.0001
Height (cm)	162.1 ± 8.6	157.5 ± 4.9	ns
BMI (kg/m ²)	22.6 ± 1.7	43.5 ± 4.8	<0.0002
Waist (cm)	75.2 ± 4.8	116.8 ± 12.2	<0.0002
circumference			
Waist-to-hip ratio	0.79 ± 0.04	0.86 ± 0.1	<0.03
Fat mass (kg)	16.6 ± 3.1	52.3 ± 10	<0.0002
Free fat mass (kg)	40.4 ± 5.4	56.5 ± 8.1	<0.0002
Systolic BP (mmHg)	117.9 ± 6.2	120.2 ± 8.5	ns
Diastolic BP (mmHg)	78.7 ± 4.8	75.5 ± 6.6	ns

BMI, body mass index; BP, blood pressure; ns, not significant.

Figure 1 (A) Plasma MCP-1 and (B) serum CRP levels in obese patients (solid bars) compared with the control group (open bars). * $P < 0.0001$.

Also, elevated MCP-1 levels are correlated with established risk factors for atherosclerosis, increased risk of death or myocardial infarction (29), and these findings reinforce the association between an inflammatory background and a poor cardiac contractile function (30, 31).

To the best of our knowledge, no direct association between MCP-1, VAT and echocardiographic abnormalities has been demonstrated. The increased MCP-1 levels in our obese women and the significant correlations with VAT area (32) and CRP levels may support a direct involvement of abdominal adiposity in systemic obesity-related inflammation and an enhancement of MCP-1 production by adipocytes may be supposed. The correlation here presented might be reinforced by the absence of confounding factors which were avoided during patient recruitment. In fact, our study was performed in young, pre-menopausal, normotensive, normocholesterolemic and drug-free patients, thus excluding the possibility that high MCP-1 concentrations may be associated with older age, hypertension, hypercholesterolemia and kidney failure (30). In addition, in our series all the patients had normal glucose tolerance and no correlation was observed between MCP-1 and the insulin sensitivity indices (HOMA and QUICKI) nor with basal glucose and insulin (data not shown) (33).

The finding that VAT and VAT/SAT significantly correlated with MCP-1 but not with SAT or total fat mass measured by BIA, supports the involvement of the omental and mesenteric compartments, which was confirmed when considering our results with stepwise

Figure 2 Correlation between plasma levels of MCP-1 and VAT area in 27 obese patients.

regression analysis. Bruun *et al.* were able to show that MCP-1 levels were higher in visceral obesity, but after adjusting for adipose-tissue resident macrophages, the difference disappeared. In our series of patients with morbid obesity, both visceral and subcutaneous adipose tissue are widely present, thus supporting our findings (12). Accordingly, a positive correlation between the reduction in MCP-1 levels and the decrease in visceral fat was reported in patients with metabolic syndrome (14). Of further interest is the observation that patients with a greater amount of visceral fat showed a greater

Table 2 Stepwise regression analysis (t value) of the association between some independent variables and MCP-1 and CRP levels in obese patients ($n = 27$).

	VAT (cm ²)	SAT (cm ²)	V/S	A.diam (cm)	Waist (cm)	WHR	BMI	BW (kg)	FM (kg)	FFM (kg)	Model R ²
MCP-1 (pg/ml) (constant value 24.7470)	0.41	1.11	5.44*	1.24	-0.12	-1.18	0.32	0.32	0.39	0.44	0.62
CRP (mg/dl) (constant value 0.42029)	2.24**	0.26	-0.39	1.23	0.13	-2.11	0.53	0.53	0.86	1.50	0.22

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; V/S, VAT/SAT; A.diam, abdominal sagittal diameter; WHR, waist-hip ratio; BW, body weight; FM, fat mass; FFM, fat-free mass.

* $P < 0.0001$, ** $P < 0.04$.

Figure 3 Correlation between MCP-1 levels and (A) posterior wall (PW), (B) left ventricular mass (LV Mass) and (C) isovolumetric relaxation time (IVRT) using the unweighted linear regression model.

MCP-1 concentration than those with a lower degree of abdominal adiposity. These data, as confirmed by stepwise regression analysis, strongly support the hypothesis that VAT is a major source of the increased levels of this cytokine.

Another issue addressed in our study concerns the involvement of the VAT-related inflammatory state with the occurrence of sub-clinical echocardiographic abnormalities. In fact, inflammatory markers are important in identifying patients with poorer contractile function and at risk of heart failure and in predicting LV remodeling (16, 28, 31). Changes in cardiac morphology and hemodynamic parameters in normotensive

Table 3 Correlation between MCP-1 and echocardiographic parameters before and after correction for increased VAT and CRP.

Echocardiographic variable	P value	
	Before	After
Posterior wall thickness (cm)	<0.005	<0.05
Relative wall thickness	<0.01	ns
LV mass (g)	<0.02	ns
Indexed LV mass (g/m ^{2.7})	<0.03	<0.05
Isovolumetric relaxation time (ms)	<0.001	<0.05
Early diastolic filling wave velocity (m/s)	<0.01	ns
Deceleration time (ms)	<0.01	ns

VAT, visceral adipose tissue; CRP, C-reactive protein; LV, left ventricle; ns, not significant.

obese patients are not new findings and the association between intra-abdominal adipose tissue and echocardiographic indices has previously been reported by us and others (15, 33).

The significant correlation between MCP-1 and echocardiographic parameters (PW, RWT, LVM and LVMh^{2.7}) obtained in our homogeneous population, even after correction for increased VAT and CRP, may support a role for MCP-1 itself in the genesis of LV morphological changes; nevertheless, the important role of VAT in influencing cardiac abnormalities and MCP-1 levels in obese patients is further sustained by the difference found in these variables when patients are divided on the basis of a VAT cut-off value of 130 cm².

As previously reported (15, 34, 35), some alterations in diastolic function parameters (such as E, IVRT and DT) were detected in obese subjects and there was a relationship between MCP-1 levels, VAT and these diastolic function indices. These observations suggest that, when there is an increase in visceral adipose tissue, a long-lasting exposition to inflammatory stimuli might be responsible for a gradual impairment of both diastolic function and cardiac morphology. On the other hand, we cannot exclude the possibility that inflammatory proteins derived from perivascular and epicardial fat might also play a role in cardiac remodeling (36).

In conclusion, our findings support the hypothesis that VAT plays an important role in determining MCP-1 levels and the inflammatory state of abdominal adiposity. It is also conceivable that MCP-1 may be implicated not only in chronic, low-grade obesity-related inflammation but also in VAT-related subclinical echocardiographic abnormalities.

Acknowledgements

This work was partially supported by grants from FIRST 60%, Rome. We thank Federica Ermetici, Luisa Molinari, Daniele Passoni for their technical assistance.

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Received 8 June 2005

Accepted 1 September 2005