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**Waist circumference adds to the variance in plasma CRP levels in elderly patients
with metabolic syndrome**

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ABSTRACT

Background

CRP, a non specific marker of inflammatory status, is associated with cardiovascular disease risk factors and may be an important feature of the Metabolic Syndrome (MSX) in middle aged subjects.

Objectives

We assessed the relationship of CRP levels with specific components of MSX and other potential determinants in apparently healthy elderly subjects living in the South of France.

Methods

In the framework of the population-based POLA (Pathologies Oculaires Liées à l'Age) study, performed on 2404 subjects aged 60 years or more, we measured plasma CRP. All subjects with known systemic inflammatory diseases such as chronic bronchitis, cardiovascular disease, diabetes and those who were on systemic steroid therapy as well as subjects with CRP >10mg/l were excluded from the analysis, leaving 1709 subjects for the statistical analyses. The metabolic syndrome was defined according to NCEP criteria. Other potential determinants were assessed through interviewer-based questionnaire.

Results

We grouped subjects into three categories based on the 75th and 25th percentiles corresponding to 3.05 and 0.82 respectively. We compared subjects in the highest quartile i.e with CRP \geq 3.05 mg/l with those in the two intermediate quartiles i.e. with $0.82 < \text{CRP} < 3.05$ and those in the lowest quartile i.e. with CRP <0.82 mg/l according to gender. MSX, which had a prevalence of 31%, was significantly associated with elevated CRP. Among MSX components, the strongest positive

association with the highest quartile of CRP was with waist circumference in males as well as females (age adjusted OR = 3.06, 95 % confidence interval (CI): 1.82 - 5.14 and OR=7.04, 95 % confidence interval (CI): 4.79-10.34 respectively). Each components of MSX such as abnormal fasting plasma glucose (OR=2.90, 95 % CI: 1.69 - 4.99), triglycerides (OR=1.96, 95 %: .1.30-2.96), HDL-cholesterol (OR=2.31, 95 % CI: 1.61-3.30), and blood pressure (OR=1.66, 95 % CI:1.12-2.45) were significantly associated with high CRP in elderly women only. In men, only current smoking was significantly associated with high CRP (OR=1.52, 95 % CI: 1.04 -2.2). In multivariate analysis, waist circumference remained significantly associated with high CRP levels with a graded effect of CRP quartile whatever the gender. In men, current and former smoking remained significantly associated with CRP levels. In women, the association observed in univariate analysis with fasting glucose or hypertension did not reach statistical significance in the multivariate analysis while only a weak association could be observed with lipid parameters such as TG and HDL cholesterol.

Conclusion

In conclusion, abdominal adiposity adds to the variance in plasma CRP levels in elderly patients with metabolic syndrome. This suggests that weight loss or other interventions targeted on adipocyte-related inflammation may represent an important means to prevent subclinical inflammation in the elderly, bearing a high risk for cardiovascular disease.

INTRODUCTION

C-reactive protein (CRP) is one of the most sensitive acute phase proteins and is widely used to evidence and estimate the severity of acute inflammation. Low-grade systemic inflammation associated with moderate increase in CRP is now recognized as a strong and independent predictor of cardiovascular risk in middle-aged subjects, and may be an important feature of the Metabolic Syndrome (MSX) and development of type 2 diabetes[1-4].

Several studies have demonstrated relationships between CRP and individual components of the MSX but the role of CRP in the pathogenesis of MSX is unclear. The classic dogma that CRP is produced exclusively in liver is challenged by recent data on the extrahepatic production of CRP in different cells including atherosclerotic lesions (especially by smooth muscle cells and macrophages), the kidney, neurons, and alveolar macrophages [5]. Interestingly, adipose tissue has been shown to produce cytokines such as TNF α and IL6, and could also contribute to the production of CRP.

In contrast to middle-aged subjects, studies in elderly are more likely to be confounded by chronic conditions such as cancer, bronchitis, arthritis, atherosclerosis or sub clinical diseases. Indeed, CRP levels increase significantly with age in both genders and the CRP median in subjects aged >65 years is twice as high as in middle-aged subjects [6] leading to confounding clinical interpretation of moderately elevated CRP levels. However, the relationship between CRP and cardiovascular disease has been previously reported in the elderly [7]. The relation between circulating levels of inflammatory markers such as IL6, TNF α , and CRP and the risk for cancer have been reported recently in an aged cohort (ages 70-79 years). The relationship with CRP seemed be site-specific, and was stronger with cancer

mortality than with cancer incidence [8]. In this context, the assessment of the determinants of CRP in the elderly is of particular interest. Few studies are currently available in this field [6, 9-10]. All reported an increase of CRP level with BMI as well as an increase in mortality with elevated CRP level. More recently MSX was reported to be associated with increased CRP levels in older adults [11].

We therefore assessed the relationship of CRP levels with specific components of MSX and other potential determinants in a population-based study of apparently healthy elderly subjects living in the South of France.

POPULATION AND METHODS

Study population

The POLA (Pathologies Oculaires Liées à l'Age) study is a prospective study, aiming at the identification of the risk factors of age-related eye diseases (cataract, age-related macular degeneration). The methods of this study have already been published elsewhere [12]. Briefly, inclusion criteria were: 1) being a resident of Sète (South of France); 2) being aged 60 years and over. According to the 1990 population census, there were almost 12,000 eligible residents, from which our objective was to recruit 3,000 participants. The population was informed of the study through the local media (television, radio and newspapers). We also contacted 4,543 residents individually by mail and telephone, using the electoral roll. Between June 1995 and July 1997, we recruited 2,584 participants.

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for the participation in the study. The design of this study has been approved by the Ethical Committee of Montpellier's University Hospital.

The participants underwent an ophthalmologic examination, an interviewer-

based questionnaire and a fasting blood sample.

Biochemical data

Fasting blood samples were collected at home, by a nurse, on the morning of the examination, between 7:00 AM and 8:15 AM. Biologic measurements include measurements on plasma (glucose, cholesterol, triglycerides, vitamin A, E and C, glutathione peroxidase) and on red blood cell (reduced glutathione, superoxide dismutase). Plasma triglycerides (TG) and total cholesterol levels were measured by routine enzymatic methods (Boehringer Ingelheim, Ingelheim, Germany). Plasma high-density lipoprotein cholesterol (HDL-C) was assayed in the supernatant after precipitation of apolipoprotein B-containing lipoproteins by magnesium phosphotungstate (Biomérieux kit).

In 2001, we performed a new series of biochemical measurements from the plasma samples collected at baseline and kept frozen at -80°C . Plasma albumin, prealbumin, orosomucoid and highly sensitive C-reactive protein (CRP, from 0.5 to 20 mg/l) was determined by latex-enhanced immunoturbidimetric method on a Olympus AU2700 biochemistry analyser (Rungis, France). Serum Protein Multi-calibrator and System Reagent particularly for CRP latex (CRP, OSR 6185) was from Olympus (Rungis, France). Calibration for CRP was performed once a week and once a fortnight respectively. The total intra assay and the total inter assay variation coefficients for serum CRP, the CV intra assay and inter assay were 3.3 % and 2.6 % respectively [13]. According to a previous study on intra-individual variability [14] and to the recommendations of the American Heart Association [15], CRP >10 mg/l were excluded in from the statistical analysis.

Interview data

Data were collected by trained study personnel. A standardized interview was

performed to assess: socio-demographic variables (marital status, educational level...); medical history (treated hypertension, cardiovascular diseases, diabetes...); all medications currently used; lifestyle factors (smoking, physical exercise, sunlight exposure). The interviewer then measured height, weight, waist and hip circumferences, systolic and diastolic blood pressures.

Body mass index (BMI) was defined as: $\text{weight}/(\text{height}^2)$ in kg/m^2 . Waist circumference was measured at the umbilicus (in centimeters). Sedentarity was defined by light household activities (coded as light/moderate/heavy) associated with less than 30 minutes per day of sport activities (mainly walking or cycling).

Definition of Metabolic Syndrome according to National Cholesterol Education Program (NCEP) :

Identification of MSX conformed to the definition used by the National Cholesterol Education Program (NCEP) [16], namely when three or more of the following five risk determinants were present :

- Fasting plasma glucose ≥ 6.1 mmol/l (110 mg/dl)
- Abdominal obesity :
 - waist circumference :
 - men $>102\text{cm}$
 - women $>88\text{cm}$
- Serum TG ≥ 1.70 mmol/l (150 mg/dl) or fibrate treatment
- Low HDL cholesterol or fibrate treatment
 - <1.03 mmol/L for men (40 mg/dl)
 - <1.29 mmol/L for women (50 mg/dl)
- Blood pressure ≥ 130 or 85 mmHg or treated hypertension

Chronic diseases

Coronary heart disease (CHD) was defined as the presence of at least of the following : 1) self-reported history of myocardial infarction or angina pectoris confirmed by medications (beta-blockers, nitrates, calcium channel blockers, potassium channel openers, molsidomin, bepridil); 2) no self-reported history of myocardial infarction or angina pectoris but past coronary artery bypass and angina pectoris medications (beta-blockers, nitrates, calcium channel blockers, potassium channel openers, molsidomin, bepridil); 3) no self-reported history of acute or chronic CHD but specific angina pectoris medications (nitrates, potassium channel openers, molsidomin, bepridil); 4) self reported history of myocardial infarction and aspirin medications.

Diabetes was defined as self-reported history of diabetes confirmed by current antidiabetic therapy and/or fasting blood glucose ≥ 7 mmol/l [17].

Asthma or chronic bronchitis was defined by self reported history of asthma or chronic bronchitis, confirmed by use of specific medications.

Missing data

Among the 2584 participants, some data were missing in the standardized interview for 25 subjects. In addition, 48 subjects had some missing data in the initial set of biochemical variables (lipids, glucose...), mainly because of refusal of blood sampling or technical failure. Other 108 subjects had some missing data in the biochemical measurements performed in 2001. This is mainly because of missing tubes in the plasma collection, due to insufficient quantity of blood sampling.

Statistical analyses

All subjects with known systemic inflammation such as chronic bronchitis (n=69), CHD (n= 212), diabetes (n= 224) and those who were on systemic steroid

therapy (n = 7) as well as subjects with CRP >10mg/l (n= 182) were excluded from the analysis, leaving 1709 subjects for the statistical analyses.

General characteristics of the participants from the POLA study were compared between men and women using chi-square (or a Fisher's test when needed) for categorical variables. For the CRP considered as a continuous variable, the distributions in the two groups were tested with Shapiro-Wilk statistic and were skewed. Thus, the relationship between CRP and gender was studied using the Mann-Whitney test (Table 1). To explore the graded influence of the CRP, subjects were grouped into three categories based on the 25th and 75th percentiles. We compared subjects in the highest quartile with those in the intermediate quartiles and those in the lowest quartile.

Multinomial logistic regression models were employed to model the relationship between the CRP levels with more than two categories, and each of the potentials determinants. Models were adjusted for age which is commonly linked to both exposure and the CRP levels. The results were expressed using Odds-ratios (OR) and their 95% confidence intervals (CI) (Table 2). Then, associations between potentials determinants and CRP levels with $p < 0.20$ in the age-adjusted model were included in a multivariate multinomial logistic regression model (Table 3).

Significance was set at $p < 0.05$. SAS software was used for statistical analysis.

RESULTS

General characteristic of the samples

Table 1 shows the characteristics of the participants from POLA Study included in the present analysis (i.e. without diabetes, coronary heart disease, systemic corticosteroid therapy, CRP>10 mg/l). The median age of both men and women was 69.3 years with a range of [60.0-92.9]. The proportion of women and men

in different age groups was not different. CRP was not statistically different between men and women. High CRP was defined as CRP levels greater than 75th percentile corresponding to 3.05 mg/l in this population. The values for the 25th and 50th percentiles of CRP were 0.82 and 1.61 mg/l respectively. Deliberately, we grouped subjects into three categories based on the 75th and 25th percentiles and we compared subjects in the highest quartile i.e with $CRP \geq 3.05$ mg/l vs those in the two intermediate quartile i.e. with $0.82 < CRP < 3.05$ and those in the lowest quartile i.e. with $CRP < 0.82$ mg/l.

MSX was present in 31.5% of the individuals studied (Table 1), without significant differences between genders. Frequency of sedentarity was also similar in men and women, while, as expected, smoking and higher education were more frequent in men.

Age adjusted analysis

Table 2 shows the age adjusted associations of high CRP values with each component of MSX based on NCEP, sociodemographic data and lifestyle parameters according to gender.

MSX defined according the NCEP was significantly associated with an increase of CRP levels. The odd ratio (OR) associated to MSX increased across quartiles of CRP, showing a graded relationship of MSX with CRP. The relationship between CRP levels and component of MSX appears different in men and women. Waist circumference was significantly associated with high CRP levels in men (OR=3.06 [1.82-5.14]) but this relationship is dramatically enhanced in women leading to an OR of 7.04 [4.79-10.34]. While all parameters of the MSX were significantly associated with high CRP in women, for men only a significant

association was observed with current and former smoking with a consistent OR across categories of CRP. With respect to lifestyle, none association could be observed with sedentarity or educational level in both genders.

Whatever the gender, significant differences were reported between the increase of CRP values and subjects presenting 0, 1, 2 3 or more disorders on NCEP criteria. OR was consistent across categories of CRP and number of components in men and in women. The OR for 3 components or more between the intermediate quartiles of CRP and lowest quartile in men or women was nearly the same (2.87 95%IC [1.34-6.14] and 2.85 95%IC[1.73-4.41] respectively). However the OR for the highest versus the lowest quartile of CRP in presence of 3 components or more was dramatically enhanced in women (OR=7.40 95%IC [3.89-14.07]) when compared to men (OR=2.38 95%IC [1.02-5.59]).

Multiple regression analysis

Results of the multiple regression analysis are presented in table 3. The variables showing an association ($p < 0.20$) with CRP in Table 2 were included in a multinomial logistic regression model. In both genders, waist circumference remained significantly associated with high CRP levels with a graded effect of CRP. In men, current and former smoking remained significantly associated with CRP levels while only a trend could be observed with blood pressure but not with TG. In women, the association observed in univariate analysis with fasting glucose or hypertension did not reach significant in the multivariate analysis while only a weak association could be observed with lipid parameters such as TG and HDL cholesterol.

DISCUSSION

In this elderly population, MSX is associated with increased CRP levels. Among components of MSX, waist circumference is clearly associated with CRP levels whatever the gender suggesting that visceral obesity adds to the variance in CRP levels in elderly subjects with MSX. By contrast other components such as TG or HDL cholesterol show only minor or even no association with CRP levels in elderly men with MSX. The variance in plasma CRP levels in elderly patients with metabolic syndrome is mainly due to waist circumference.

Definition of MSX and prevalence in an elderly French population

The MSX has emerged as a clinical condition associated with an enhanced risk of conversion to type 2 diabetes [2] and cardiovascular disease [3-4]. But several problems have been noted with the definition of metabolic syndrome. The term of « metabolic syndrome » was first defined as a method for identifying subjects at increased risk of both diabetes and cardiovascular disease, who could be candidates for a specific treatment [18-19]. However, there is currently no specific treatment of the metabolic syndrome other than the treatment of its individual components, and one may doubt of the clinical relevance of this syndrome.

Among the main definitions, the more frequently used is National Cholesterol Education Program (NCEP ATP-III) [16] because it requires neither an oral glucose tolerance test nor fasting insulin or microalbuminuria by contrast to WHO definition [20-21]. More recently other organizations have developed similar definitions among which the Diabetes Predicting Model [22] and the Framingham Risk Score [23] which seem to be more effective at predicting diabetes and cardiovascular disease. In these predictive models, risk factors are treated as continuous variables in opposition to

NCEP ATP III. Since CRP, and other major determinants of the MSX do not follow a normal distribution, the analysis as continuous variables seems less appropriate than quartile determination as used in the present study. Thus in the absence of specific definition in the elderly, we have chosen NCEP as a definition of MSX as previously reported in the few studies in elderly subjects [24-25]. Even if NCEP criteria can be criticized, it is a commonly accepted definition and has been also validated by the European Group for The Study of Insulin Resistance [26].

MSX prevalence in our group of French elderly was estimated to be 31.5% and was similar for men (32.82%) and women (30.65 %). This result fits previous estimates of the prevalence of the MSX in a middle-aged southern European population [27] and more specifically in France [28]. In older persons, the prevalence was reported to be higher in women than in men particularly after 70 years [29]. As previously reported, the prevalence seems different in the United States than in Europe [30] and hypertension is the most frequent feature of MSX in France [31], by contrast to adiposity in the United States.

Inflammation is linked to components of MSX per se in univariate analysis

Emerging evidence now supports the concept that systemic inflammation is associated with the development and complications of MSX in middle aged subjects [3, 32-35]. By contrast, little is known in the elderly about the relative contribution of individual factors such as obesity, dyslipidemia and hypertension or the concomitant effect of all these components. Our data clearly demonstrate the link between CRP levels and MSX in elderly subjects, extending previous observations regarding this association in a tri-ethnic American population including subjects between 40 to 69 years [36-37]. Indeed, in our European population univariate analysis demonstrates

that in the elderly women over 80 years each component of MSX is a significant determinant of CRP level (Table 2).

Adiposity (in particular waist circumference in men and women with an OR=3.06 and 7.04 respectively) was more strongly associated with moderately elevated CRP than the other components of MSX (glucose disorder, lipid parameters, blood pressure). Obesity appears as a heterogeneous condition and fat distribution is thought to play a major role in co-morbidities and correlates with the cluster of MSX [38-39]. As previously reported in epidemiological studies, abdominal adiposity defined either with waist hip ratio or waist circumference is an important determinant of micro-inflammation in middle aged subjects [40] as well as in the elderly [41].

A gender specificity was observed in elderly women for fasting glucose, lipid metabolism and hypertension. The relationship between fasting glucose and CRP has been previously reported in middle aged or elderly women [32, 42] or in non smoking elderly subset [43]. However, the women specificity observed here for TG, HDL-C and hypertension was not reported in previous studies [44 46].

By contrast the strong association between cigarette smoking and inflammation was observed only in men. Similar significant association was described by several authors [6, 9, 43] with different findings. Lifetime smoking exposure has been reported to be more strongly associated with CRP values than smoking status itself [43]. But the current smokers were combined with past-smokers into a single group of ever-smokers, possibly obscuring the relationship between cigarette smoking and CRP level. More recently CRP was found higher among current smoker than former smokers and never smokers [47]. These findings are

consistent with our results since current smoking was associated more strongly with high CRP levels in our population than not former smoking.

Sociodemographic data and lifestyle, classically related to MSX, could explain part of variance in CRP levels. Although a positive correlation between age and CRP concentration was reported in middle-aged subjects [44, 48], we did not evidence such a relationship in this elderly population, in agreement with Stranberg et al [6]. In addition, in this home-living elderly cohort, sedentarity and educational level were not associated with high CRP. However we can not rule out that the weakness of the relationship between the inflammation and socioeconomic markers may in part be masked in older age by the common occurrence of longstanding diseases in all socioeconomic groups. [49].

Finally, CRP levels increased with the increasing number of MSX components in all subjects, as found in other studies in middle-aged subjects [4, 35, 50].

Waist circumference adds to the variance in plasma CRP levels in elderly patients with metabolic syndrome

In multivariate analysis, adiposity was significantly associated with CRP levels whatever the gender. By contrast, Insulin resistance (IR) was not associated with inflammation while only a weak association could be evidenced with TG and HDL cholesterol in women. IR was initially recognized as the underlying event of MSX leading to biological manifestations such as a compensatory increase in plasma concentrations of insulin, glucose intolerance and hyperglycemia, dyslipidemia characterized by hypertriglyceridemia and decrease of HDL-cholesterol [51-52], and an increased tendency for thrombosis (associated with elevated PAI-1) [53]. IR has also been reported to drive high levels of CRP in overweight subjects [36]. By contrast there is now increasing recognition that abdominal adiposity at least

conspires with IR or is the leading cause to the development of MSX. In agreement with our results, adipose tissue is now recognized as an important modulator of the inflammatory response. Indeed, adipocytes synthesize and release a large number of adipokines, both with anti-inflammatory activity, such as adiponectin, and pro-inflammatory activity, such as TNF α , IL-6 or CRP [50, 54]. It is interesting to note that adiponectin may have a direct effect on lipoprotein metabolism in particular on HDL cholesterol, which may be independent of insulin [55]. More recently Calabro et al. [56] demonstrated that the production of CRP by human adipocytes is due to stimulation by several pro inflammatory cytokines. Thus, obesity-mediated cytokine production is presumed to be an important mechanism for CRP increase [57]. Although the contribution of obesity-induced cytokines production in MSX induced-inflammation remains unclear, it is tempting to speculate that increase in CRP levels could be a reliable biochemical marker likely to reveal the imbalance between these pro- and anti-inflammatory adipokines. Interestingly, increase in pro-inflammatory and decrease in anti-inflammatory adipokines have been involved in metabolic syndrome complications such as conversion to type II diabetes or cardiovascular diseases [58-59]. The major importance of adiposity in the multivariate analysis is in agreement with a recent study of Timpson et al. [60] using Mendelian randomisation approach, suggesting that the association between CRP and MSX might be affected by reverse causation or confounding, in particular by obesity [61]. It has been shown that cytokines production by adipose tissue could be pharmacologically modulated [56] suggesting that obesity linked inflammation could be a therapeutic target for decreasing risk for cardiovascular disease or diabetes.

CONCLUSION

Epidemiological studies [32, 62] have strongly suggested that CRP is an independent predictor of diabetes and CHD. In the present study, we confirmed a strong association of CRP with MSX components. Waist circumference adds to the variance in plasma CRP levels in elderly patients with metabolic syndrome. In this context our study confirms and extends previous observations demonstrating that the relationship between CRP and MSX is also observed in an elderly European population particularly in elderly women. This suggests that weight loss or other interventions targeted on adipocyte-related inflammation may represent an important means to prevent subclinical inflammation in the elderly, bearing a high risk for cardiovascular disease.

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