Interpretation of circulating C-reactive protein levels in adults: Body Mass Index and gender are a must

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S U M M A R Y

Objective: The recently demonstrated association between C-reactive protein (CRP) level and body mass index (BMI) raised the question of the link between CRP and the degree of obesity. In the present study, we measured CRP in a healthy population with a wide range of BMI in order to appreciate the influence of overweight in the interpretation of CRP results in clinical use.

Method: Blood donors, aged from 19 to 65 years, were included in the study. According to BMI, subjects were classified into 3 groups: A (BMI < 25 kg/m², n = 611); B (25-30, n = 147); C (> 30, n = 34).

Results: CRP values were different among women and men. CRP progressively increased with BMI in women. These results clearly showed that average level of CRP was quite different according to BMI and gender of the subjects and generated different normal ranges of CRP expressed in mg/L (median, 75th percentile): Group A: women: 0.44, 0.93; men: 0.40, 0.79, Group B: women: 1.28, 1.84; men: 0.84, 2.17, Group C: women: 3.61, 7.21; men: 1.16, 3.08.

Conclusion: Our results suggest that for an inflammatory disease diagnosis, a CRP concentration of 5 mg/L is normal for obese women but is five times the 75th percentile for normal people.

Key-words: CRP - BMI - Gender - Obesity - Inflammation.

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R É S U M É

Relation entre la CRP circulante, le sexe et l’index de masse corporelle

Objectif : Ces dernières années ont vu émerger la possibilité d’une association entre la Protéine C réactive (CRP) circulante et le degré d’obésité, mesuré par l’Index de Masse Corporelle ou IMC. Dans cette étude, nous avons mesuré les concentrations sériques de CRP chez des sujets sains, qui présentaient un large éventail d’IMC, afin d’évaluer l’influence de l’obésité sur l’interprétation des concentrations de CRP en pratique clinique.

Méthode : Des donneurs de sang, âgés de 19 à 65 ans ont été inclus dans l’étude et ont été séparés en 3 groupes, en fonction de leur IMC : Le groupe A (IMC< 25 kg/m², n = 611) ; le groupe B (25 à 30 kg/m², n = 147) et le groupe C (IMC > 30 kg/m², n = 34).

Résultats : Les concentrations de CRP étaient significativement différentes chez les hommes et chez les femmes. Elles augmentaient progressivement avec l’IMC dans la population féminine. Ces résultats montrent que les valeurs de CRP étaient différentes selon l’IMC et le sexe des sujets et permettaient d’établir de nouvelles valeurs usuelles pour la CRP : valeur médiane. 75e percentile, exprimées en mg/L. Dans le groupe A : 0,44 ; 0,93 (femmes), 0,40 ; 0,79 (hommes). Dans le groupe B : 1,28 ; 1,84 (femmes), 0,84 ; 2,17 (hommes), dans le groupe C : 3,61 ; 7,21 (femmes), 1,16 ; 3,08 hommes.

Conclusion : Ces résultats suggèrent que pour le diagnostic d’un syndrome inflammatoire, une concentration circulante de CRP à 5 mg/L peut être normale chez les femmes obèses, mais qu’elle équivaut à cinq fois le 75e percentile chez un sujet normal.

Mots-clés : CRP - IMC - Sexe - Obésité - Inflammation.

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The implication of low-level inflammation as an important factor of atherosclerosis is now well admitted [1]. Indeed, to evaluate inflammation in atherosclerosis, several epidemiological studies have evaluated circulating markers of inflammation to predict the risk of vascular damage. The recent use of high sensitivity C-Reactive Protein (CRP) assays allowed the demonstration of an association between CRP levels and prediction of risk of myocardial infarction, stroke and peripheral arterial disease among apparently healthy subjects [2-5] or among high-risk patients [6, 7]. However, clinical application of CRP measurements requires a better knowledge of normal range values and determination of cut-off levels for diagnosis of both inflammation and vascular risk detection. This is particularly of interest in low-risk populations without well-known cardiovascular risk factors.

Among the various studied populations (healthy men and women, elderly subjects, with or without risk of cardiovascular disease (CVD)), a strong association between CRP and Body Mass Index (BMI) was demonstrated in several studies [8-14], suggesting a possible role for adipose tissue in the elevation of CRP. In agreement with this hypothesis, we and others found that adipose tissue might play a role in the regulation of circulating CRP concentration via interleukin-6 (IL-6) production [15, 16]. Furthermore, an elevation in IL-6 levels was observed among obese subjects [17] or apparently healthy adults presenting a risk of CVD [18]. Moreover, a greater prevalence of obesity was observed among patients at high risk of myocardial infarction [18]. In recent studies, weight loss was demonstrated to reduce CRP [11, 19] or IL-6 levels [20, 21]. These data suggest that the interpretation of CRP levels requires information about the degree of obesity of patients.

We measured circulating CRP concentrations in a healthy population with a wide range of BMI. Our results confirm the link between overweight or obesity and CRP levels and pointed out the necessity to interprete CRP results according to gender and BMI.

**Methods**

**Patients**

A total of 792 blood donors retrospectively selected from our database [22] was included in the study. They were 462 men and 330 women, aged from 19 to 65 years. Based on a medical questionnaire and on laboratory measurements including bilirubin, aminotransferases, GammaGlutamyl-Transferase, total cholesterol and triglycerides, they were classified as healthy. Exclusion criteria were an history of acute or chronic inflammatory disease, drug or hormonal therapy at the time of the study.

The patients were classified into 3 groups, according to their BMI: group A (BMI < 25 kg/m²); B (25-30 kg/m²); C (> 30 kg/m²).

**Methods**

Concentrations of CRP were assessed in frozen serum samples (~ 80°C). CRP levels were measured with a highly sensitive immunoassay (detection level: 0.17 mg/L) on a BNII nephelometer (Dade-Behring, Paris, France) using monoclonal antibodies coated with latex particles. The coefficient of variation at CRP concentrations ranging from 0.17 to 11 mg/L was less than 5%.

**Statistical analysis**

All biochemical factors were transformed into decimal logarithm, when distribution of values was skewed. The univariate associations between BMI or age and CRP expressed in decimal logarithm were assessed by Pearson’s correlation coefficient for quantitative factors in the whole population and by non parametric Spearman’s correlation in the subgroups. Multivariate analysis by General Linear Model was performed to select parameters independently associated with CRP.

Differences in CRP values between patients classified according to age, sex or smoking habits were assessed by Student’s t test. Non parametric Kruskal-Wallis test was performed to assess differences in CRP levels between patients classified according to their BMI and gender. Non parametric Mann-Whitney test was performed to compare CRP levels between 2 groups.

A P value inferior to 0.05 was considered as significant.

**RESULTS**

Among 792 (462/330) patients (men/women), there were 318 (186/132) smokers and 474 (276/198) non-smokers. BMI ranged from to 16.0 to 48.7 kg/m². Patients were classified into 3 groups, according to well-admitted BMI cut-offs for defining normal, overweight and obese people. There were Group A: BMI < 25 kg/m², n = 611, Group B: BMI ranging from 25 to 30 kg/m², n = 147 and Group C: BMI > 30 kg/m², n = 34.

The biochemical and clinical characteristics of the patients, classified according to their BMI, are reported in Table I. Age and CRP were statistically different in the three groups.

Mean values (SD) in CRP concentrations were 1.00 (1.46) mg/L for men and 1.26 (1.81) mg/L for women. Among smokers (men/women), mean (SD) CRP values were 1.23 (1.74) mg/L (1.11 (1.55)/1.40 (1.97)). Among non-smokers (men/women), mean (SD) CRP values were 1.03 (1.54) mg/L (0.93 (1.41)/1.16 (1.70)). As shown in Table II, there was a significant difference in CRP levels between men and
smoking women

status, the same results were observed, except for non-

patients were classified according to gender and smoking

–

values than younger patients (t = 2.078, p < 0.05). When

Patients aged over 30 years had significantly higher CRP

in the whole population (r = 0.429, p < 0.0001), as well as in

women (z = 0.83, p < 0.0001) and men (z = 9.12, p < 0.0001) and non-smokers

(z = 6.37, p < 0.0001). When patients were classified according
to gender and age (less than 30 and over 30 years), CRP

remained associated with BMI in all the groups (p < 0.0001).

However, when patients were separated according to
	heir BMI, CRP remained associated with BMI in patients

with BMI < 25 kg/m² (z = 5.536, p < 0.0001) or superior to

30 kg/m² (z = 2.805, p = 0.005) but not in patients with BMI

ranging from 25 to 30 kg/m².

Multivariate analysis demonstrated that BMI (t = 12.14, p < 0.0001), smoking habits (t = 3.21, p < 0.002) and age

(t = 2.63, p < 0.009) were independently associated with

CRP, which explained 16.5% of variation in CRP levels. A
tendency to an independent association between gender and

CRP was noted (t = 1.92, p = 0.056). Figure 1 illustrates the increase in CRP values with BMI

in the whole population (Fig 1a) and according to gender in

the women group (Fig 1b). Indeed, non parametric Kruskal

Wallis test demonstrated that there was a significant differ-
ence in CRP values between patients classified according to
	heir BMI (H = 104.9, p < 0.0001). When patients were further

classified according to gender, CRP values increased

Effects of age on CRP levels

CRP concentration was significantly associated with age

in the whole population (r = 0.217, p < 0.0001) as well as in

women (z = 4.41, p < 0.0001) and men (z = 4.61, p < 0.0001) and in smokers (z = 5.22, p < 0.0001) and non-smokers

(z = 4.91, p < 0.0001).

Patients aged over 30 years had significantly higher CRP

values than younger patients (t = −5.552, p < 0.0001). When

patients were classified according to gender and smoking

status, the same results were observed, except for non-

smoking women (Tab II).

Although there was only a tendency for CRP levels to be

significantly different among smokers and non smokers in

the whole population, CRP levels were higher in smokers

compared to non-smokers among women aged over 30 years

(t = −2.078, p < 0.05).

Effect of BMI on CRP levels

A strong association was found between CRP and BMI

in the whole population (r = 0.429, p < 0.0001), as well as in

women (z = 8.28, p < 0.0001) and men (z = 7.66, p < 0.0001)

and in smokers (z = 9.12, p < 0.0001) and non-smokers

(z = 6.37, p < 0.0001). When patients were classified accord-
ing to gender and age (less than 30 and over 30 years), CRP

remained associated with BMI in all the groups (p < 0.0001).

However, when patients were separated according to
	heir BMI, CRP remained associated with BMI in patients

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CRP, which explained 16.5% of variation in CRP levels. A
tendency to an independent association between gender and

CRP was noted (t = 1.92, p = 0.056).

Table I

Patients characteristics.

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt; 25 kg/m²</th>
<th>25-30 kg/m²</th>
<th>&gt; 30 kg/m²</th>
<th>P value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 years</td>
<td>29 ± 11*</td>
<td>37 ± 12*</td>
<td>43 ± 14*</td>
<td>&lt; 0.05</td>
<td>31 ± 12</td>
</tr>
<tr>
<td></td>
<td>(18-64)</td>
<td>(19-63)</td>
<td>(19-65)</td>
<td></td>
<td>(18-65)</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>21.6 ± 1.8*</td>
<td>26.8 ± 1.3*</td>
<td>35.0 ± 4.8*</td>
<td>&lt; 0.0001</td>
<td>23.1 ± 3.7</td>
</tr>
<tr>
<td>CRP</td>
<td>0.83 ± 1.23*</td>
<td>1.74 ± 2.05*</td>
<td>3.46 ± 2.76*</td>
<td>&lt; 0.0005</td>
<td>1.11 ± 1.62</td>
</tr>
</tbody>
</table>

Results are presented as mean ± standard deviation. * statistically different from the two other groups. The highest P value considered as significant is indicated.

| Table II

CRP values according to age, gender and smoking habits of patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (n = 330)</td>
</tr>
<tr>
<td></td>
<td>Smokers</td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>1.23 ± 2.12</td>
</tr>
<tr>
<td></td>
<td>n = 73</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>1.62 ± 1.76*§</td>
</tr>
<tr>
<td></td>
<td>n = 59</td>
</tr>
<tr>
<td>Total</td>
<td>1.40 ± 1.97</td>
</tr>
<tr>
<td></td>
<td>n = 132</td>
</tr>
</tbody>
</table>

Results are presented as mean ± standard deviation. * statistically different from the patients aged less than 30 years (p < 0.05). § statistically different from the non-smokers (p < 0.05). ‡ statistically different from the men (p < 0.05).
with BMI among women (H = 65.76, p < 0.0001). However, among men, Mann and Whitney test demonstrated that CRP levels did not significantly differ between Group B and Group C.

These associations generated different distribution of CRP values in the whole population and according to their BMI and gender, as described in Table III.

In the whole population studied, the 95th percentile for CRP values was 4.49 mg/L. When patients were classified according to their BMI, the 95th percentile was 3.32 for patients with a BMI < 25 kg/m², whereas it became 8.40 for patients with a BMI > 30 kg/m². The separation of patients according to BMI and gender lead to the following values for the median (75th percentile): 0.40 (0.79) mg/L and 1.16 (3.08) mg/L for men with a BMI < 25 kg/m² and BMI > 30 kg/m², respectively. Among women, the median (75th percentile) for CRP values was 0.44 (0.93) mg/L and 3.61 (7.21) mg/L for BMI < 25 kg/m² and > 30 kg/m², respectively.

**Discussion**

This study has identified factors associated with CRP variability in a general population with a wide range of BMI. By using these factors, i.e., gender and BMI, we suggest new reference values for diagnosis of inflammation in a general population.

We found the highest CRP levels in overweight or obese subjects, which was in agreement with a possible link between circulating CRP concentrations and obesity. Indeed, several studies undertaken among various populations, i.e., middle-aged women or men [14, 13, 5, 12, 8, 6, 10] or children [23] have already described such an association. Our
Table III

<table>
<thead>
<tr>
<th>Distribution of CRP values in the whole population and according to BMI and gender of patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Classification according to BMI</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
</tr>
<tr>
<td>BMI 25-30</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
</tr>
<tr>
<td>Classification according to BMI and gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
</tr>
<tr>
<td>BMI 25-30</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
</tr>
<tr>
<td>BMI 25-30</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
</tr>
</tbody>
</table>

The higher CRP values observed in overweight or obese patients then might be consecutive to the production of IL-6 by adipose tissue, without any inflammatory process, and therefore the stimulation of CRP production by the inflammatory cytokine [26]. Furthermore, percentage of fat mass is higher in women than in men and in older subjects than in younger ones, with comparable BMI [27]. Body fatness could then explain the differences in CRP values observed between obese men and women and between younger and older patients.

In the view of the present results, it seems that redefining new ranges for CRP reference values is important for diagnosis of inflammatory processes. Several recent papers have providing new insights in this way. Mc Connell et al. [25] suggested to take into account gender for the interpretation of CRP values, since Chenillot et al. [28] proposed both gender and age for definition of reference ranges. However, for the fist time, we included both gender and BMI, which are easily measurable parameters, in the clinical interpretation of CRP values. Our results showed that the 95th percentile of normal values given by the manufacturer (2.87 mg/L) is similar to the 75th percentile obtained in the whole population. However, it is twice lesser than the CRP values of subjects with a BMI superior to 30 kg/m². Otherwise, among subjects whose BMI is less than 25, the 75th percentile was 0.93 and 0.79 mg/L in women and men, respectively. Therefore, in inflammatory disease diagnosis, we must keep in mind that whereas a CRP concentration of 5 mg/L can be a normal value among women with a BMI superior to 30 kg/m², it is nearly five times the 75th percentile for CRP values among lean people and is probably too high for diagnosing an inflammatory process.

In conclusion, these results suggest that individual factors must be taken into account to interprete CRP values in a general population. We suggest that normal range values and upper limit of CRP concentrations must be redefined according to BMI and gender of the subjects. Further studies in larger populations or retrospective analysis from well-documented cohorts are necessary to define standardized reference values.

References


