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C-reactive Protein Associates with Metabolic Syndrome: An Improved Conventional Assay may Fit for Purpose in Population-based Analyses

Seki R [1*], Inoue K[2] and Akimoto K[3]

[1]*Teikyo University School of Medical Technology, Itabashi, Japan*

[2]*Department of Community Medicine, Chiba Medical Center, Teikyo University of Medicine, Chiba, Japan*

[3]*Akimoto Occupational Health Consultant Office, Tokyo, Japan*

Abstract

Background and Aim: The plasma C-reactive protein (CRP) is a well-studied biomarker of infection and systemic inflammation. In large prospective studies, high-sensitivity CRP (hs-CRP) has been shown to be a useful predictor of metabolic syndrome (MetS) in healthy subjects. However, the hs-CRP-based studies of the associations between CRP and MetS-relevant metrics in East Asian populations have analyzed a limited number of subjects. Several authors have also pointed out between-institution and between-reagent kit differences of hs-CRP assays. In this study, we aim to examine associations of CRP with other MetS-related metrics in the dataset of over 34,000 Japanese adults using an improved conventional CRP assay. **Methods:** A cross-sectional study was conducted using the dataset of apparently healthy individuals drawn from the general Japanese population (16,040 men; 16,439 women; mean age 51 years). We divided subjects into four groups based on CRP levels: <1, 1 to <2, 2 to <3, and 3 to <9 mg/L. We used the multivariate logistic regression analysis to examine the age/sex-adjusted odds ratio of each group for the MetS-associated conditions. **Results:** After adjustment for age and sex, the odds ratio of MetS were significantly greater in the higher CRP groups compared to the low CRP group (<1 mg/L). **Conclusions:** Consistent with recent studies using hs-CRP assay, the subjects with 1 to 2 mg/L CRP showed an increased risk for MetS, reinforcing the view that CRP is an efficient independent predictor for MetS. In the light of the financial and operational merits, our data also suggests the usefulness of improved conventional CRP assays for the percentile-based studies on the risk assessment of CRP values.

Introduction

MetS comprises a cluster of abnormalities with insulin resistance and abdominal obesity. The presence of central obesity, dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol), impaired glucose tolerance, and evaluated blood pressure is considered adequate to diagnose the syndrome [1,2]. Individuals with these characteristics commonly develop a proinflammatory state and have an increased burden of cardiovascular disease (CVD).

CRP, a hepatic acute phase protein, is a well-characterized biomarker of inflammation. Its synthesis is primarily controlled by IL-6. CRP has been used to monitor major infections, clinically evident inflammatory disorders, and endocarditis (>10 mg/L). Ridker et al. reported that a slight elevation of hs-CRP (<3 mg/L), which was previously considered to fall within the normal range, has the potential to play an important role as an adjunct for global risk assessment in primary prevention of cardiovascular disease [3]. They further showed that hs-CRP is a more significant predictor of cardiovascular events than the LDL cholesterol (LDL-Chol) level [4]. Thus, hs-CRP has been shown to improve CVD risk prediction, therefore basis of various guideline, including those from the American College of Cardiology/American Heart Association, the European Society of Cardiology recommend considering use of hs-CRP to inform treatment decisions, mainly for persons at intermediate risk [5,6]. These guidelines acknowledge its role as an established marker of future risk of CVD. Currently, 2 mg/L is a cut-off point suggested in several studies for treatment decision (see Discussion).

At present, however, both hs-CRP and improved conventional CRP assays appear to suffer from challenges in standardization. At least at the time of writing, it is not clear which of the hs-CRP assays and the conventional CRP assays yield the true value [7]. In particular, it is worrisome that the between-institution differences in hs-CRP data on similar populations have been considerably large (see Discussion) [8,9]. Another issue in hs-CRP assays is that the dynamic range is typically limited to 0.1~20 mg/L, requiring frequent sample dilutions, raising reagents cost and compromising overall usefulness in clinics [7]. It should also be noted that improved conventional CRP assays allow the measurement of 1 mg/L with CV <10% [7,10], and also show good concordance with hs-CRP data for the range near 1 mg/L [7]. Given these considerations, we analyzed the health checkup data involving the CRP values obtained by an improved conventional method and examined their associations with the MetS-related parameters.

Methods

We used a dataset derived from the health screening program performed by the Yuport Medical Checkup Center in Tokyo from April 1998 to 2006. The details of this program have been reported elsewhere [11,12]. For repeat participants, first-visit data was used for the study. After the exclusion of 1,230 subjects with medical history and 594 subjects with

CRP value >9 mg/L, the final population comprised of 32,479 subjects for the analysis (Figure 1). This study was approved by the ethics committee of Teikyo University.

Serum samples were obtained after overnight fasting were measured at the center's laboratory. According to CRP levels, we categorized these subjects into four separate groups: <1, 1 to <2, 2 to <3, 3 to 9 mg/L.

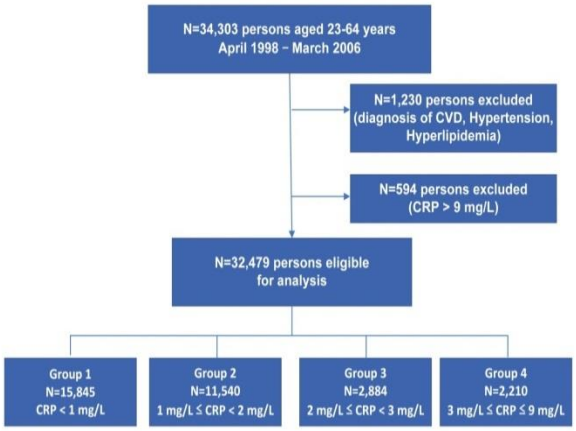

Figure 1: Enrollment of the subjects.

For measurement CRP levels, CRP-latex Seiken was used (DENKA SEIKEN Co., Ltd, Tokyo, Japan). The measurements of other parameters were done as we previously described [11-13]. Briefly, for triglyceride (TG), total cholesterol (T-Chol), and HDL-cholesterol (HDL-Chol) levels, a Toshiba TBA-40FR Autoanalyzer (Toshiba Medical Systems, Tokyo, Japan) was used. HDL-Chol was measured after selective solubilization of non-HDL lipoproteins (Daiichi Pure Chemicals Co., LTD, Tokyo, Japan). LDL-Chol levels was estimated by the Friedewald formula. HbA_{1c} levels were measured using the latex immuno-agglutinin method (Determiner hemoglobin A_{1c}; Kyowa Medex, Tokyo, Japan). The remaining parameters were measured with the methods recommended by manufacturers. Body mass index (BMI) was calculated as weight as kilograms divided by height as meters squared (kg/m^2). We defined MetS-associated conditions according to the cut point in Table 2. BMI>24 kg/m^2, fasting plasma glucose (FPG)>7 mmol/L (126 mg/dL), HbA_{1c}>6.5%, Triglycerides (TG) >1.7 mmol/L (150 mg/dL), LDL-Chol>3.6 mmol/L (140 mg/dL), HDL-Chol<1.0 mmol/L (40 mg/dL), systolic blood pressure (SBP)>140 mmHg and diastolic blood pressure (DBP)>90 mmHg.

All statistical analyses were performed using SPSS for windows 15.0 (SPSS Inc., Tokyo, Japan).

Results

The workflow for this study is schematized in Figure 1. In the original population (34,303 subjects), the mean (SD) of serum CRP concentration was 1.19 (3.55) mg/L. The mean for the men (17,102 subjects) was 1.41 (3.40) mg/L which was higher than the mean of the women (17,201 subjects), which was 0.98 (3.03) mg/L.

After the exclusion of the subjects with the conditions given in the Methods, the 32,479 subjects were classified into four groups according to the CRP level (Table 1).

	All	Categories by C-reactive protein levels			
		Group 1	Group 2	Group 3	Group 4
		CRP<1 mg/L n=15,845 (48.7%)	1 ≤ CRP<2 mg/L n=11,540 (35.5%)	2 ≤ CRP<3 mg/L n=2,884 (8.9%)	3 ≤ CRP ≤ 9 mg/L n=2,210 (6.8%)
Age (years)	51 (13)	49 (13)	53 (13)	55 (13)	54 (13)
Men, n (%)	16,040 (49.4)	6,700 (42.3)	6,300 (54.6)	1,709 (59.3)	1,331 (60.2)
Body mass index (kg/m^2)	22.8 (3.1)	21.8 (2.7)	23.5 (3.0)	24.3 (3.3)	24.3 (3.7)
Fasting plasma glucose (mmol/L)	5.4 (19)	5.3 (0.8)	5.5 (1.1)	5.7 (1.4)	5.8 (1.6)
Hemoglobin A_{1c} (%)	5.33 (0.74)	5.26 (0.79)	5.53 (1.08)	5.68 (1.38)	5.82 (1.56)
Systolic blood pressure (mmHg)	123 (18)	119 (17)	126 (18)	129 (18)	129 (18)
Diastolic blood pressure (mmHg)	75 (11)	72 (11)	76 (11)	78 (11)	78 (11)
White blood cell count (10^9/L)	5.7 (1.7)	5.3 (1.6)	5.9 (1.5)	6.3 (1.7)	6.7 (19)
Triglycerides (mmol/L)	1.27 (0.72-1.51)	1.08 (0.64-1.28)	1.40 (0.81-1.68)	1.55 (0.89-1.86)	1.55 (0.88-1.81)
Total cholesterol (mmol/L)	5.24 (0.92)	5.13 (0.89)	5.34 (0.93)	5.39 (0.95)	5.25 (0.97)
HDL cholesterol (mmol/L)	1.49 (0.38)	1.58 (0.38)	1.44 (0.37)	1.38 (0.36)	1.33 (0.35)
LDL cholesterol (mmol/L)	3.49 (0.87)	3.33 (0.83)	3.62 (0.87)	3.70 (0.89)	3.60 (0.92)
Aspartate aminotransferase (U/L)	23 (17-25)	21 (17-23)	24 (18-26)	25 (18-27)	27 (18-28)
Alanine aminotransferase (U/L)	23 (14-25)	20 (13-22)	25 (15-28)	27 (15-31)	30 (15-32)
γ-glutamyl transpeptidase (U/L)	32 (12-34)	25 (11-26)	37 (14-40)	38 (14-43)	44 (15-48)

Data are expressed as mean (SD), median (25 percentile, 75 percentile) or number (%). For all results, statistical significance was P<0.001, where P-values were for comparison of means (analysis of variance adjusted by age) or percentages (chi-square test). For comparison of means, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT) and white blood cell count was log-transformed for their skewed distributions. To convert the values of plasma glucose to mg/dL, multiply by 18. To convert the values for triglycerides to mg/dL, multiply by 88.5. To convert the values for total, low and high-density lipoprotein cholesterols to mg/dL, multiply by 38.7.

Table 1: Characteristics of 32,479 subjects stratified according to C-reactive protein levels.

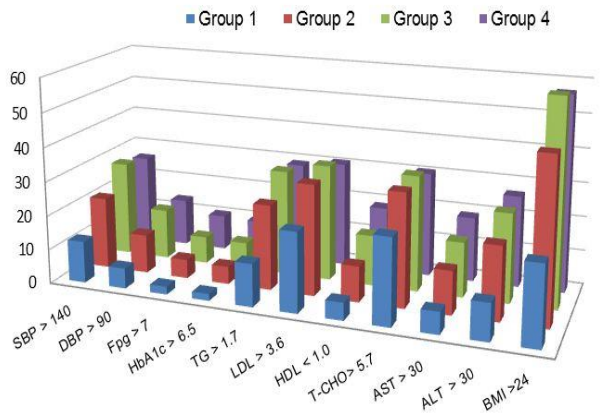

Figure 2: Proportions (%) of subjects with poorer profiles of markers associated with cardiovascular disease and metabolic syndrome in each group.

Basic characteristics of each group are shown in Table 1. Of note, the mean age and the proportion of men tended to be high in higher CRP groups. As Table 1 shows, the MetS-associated parameters (BMI, blood pressure, serum lipid and glucose) generally showed a significant association with CRP levels. For all parameters listed in Table 1, all of the group 2, 3 4 showed significant difference in comparison with group 1 ($p<0.001$) (Figure 2).

In general, the MetS-relevant parameters across the groups showed a monotonous increase (BMI, FPG, HbA_{1C}, white blood cell (WBC), ALT, AST, γ-GT) or decrease (HDL-Chol) in association with the increase of the CRP value. For some parameters (SBP, DBP, TG, and T-Chol) the difference between groups 3 and 4 was insignificant. Intriguingly, for T-Chol and LDL-Chol, the opposite trend was observed between the group 3 and 4. For example, total cholesterol showed a difference of the order of: group 1<group 4<group 2<group 3.

As shown in Table 2, our multivariate logistic regression analysis showed that all of the groups 2, 3 and 4 had a greater risk for the conditions corresponding to the MetS components compared to the group 1 as the reference. For example, the group 2, within which the CRP mean of the male subjects fell, exhibited a significant odds ratio (1.51) for the high blood pressures as well as the high BMI value, the pre-diabetic conditions, and hyperlipidemia. For both male and female subjects, compared with the groups 2 and 3, less pronounced associations with the MetS-associated conditions were observed for group 4 relative to group 1. Regarding BMI and blood pressure, the female subjects showed the higher ORs compared to the male subjects.

		Group 2 (n=11,540)	Group 3 (n=2,884)	Group 4 (n=2,210)
BMI > 24 kg/m^2	**All**	**2.46*** (2.33-2.60)**	**1.99*** (1.91-2.08)**	**1.24*** (1.22-1.27)**
	Men	2.24*** (2.08-2.41)	1.73*** (1.64-1.83)	1.20*** (1.17-1.23)
	Women	2.68*** (2.47-2.92)	2.11*** (1.98-2.26)	1.31*** (1.27-1.35)
Diabetic conditions: FPG > 7 mmol/L or HbA_{1c} > 6.5%	**All**	**1.89*** (1.68-2.14)**	**1.58*** (1.46-1.72)**	**1.25*** (1.21-1.29)**
	Men	1.78*** (1.53-2.06)	1.60*** (1.45-1.76)	1.25*** (1.20-1.29)
	Women	2.05*** (1.65-2.54)	1.50*** (1.29-1.75)	1.25*** (1.18-1.32)
Hyperlipidemia: TG > 1.7 mmol/L, LDL-Chol > 3.6 mmol/L or HDL-Chol < 1.0 mmol/L	**All**	**1.77*** (1.68-1.86)**	**1.44*** (1.39-1.51)**	**1.12*** (1.10-1.14)**
	Men	1.79*** (1.67-1.92)	1.46*** (1.39-1.54)	1.13*** (1.10-1.16)
	Women	1.63*** (1.52-1.76)	1.39*** (1.30-1.48)	1.09*** (1.06-1.13)
High blood pressure: SBP > 140 mmHg or DBP > 90 mmHg	**All**	**1.51*** (1.42-1.62)**	**1.43*** (1.36-1.51)**	**1.13*** (1.11-1.16)**
	Men	1.49*** (1.36-1.63)	1.36*** (1.27-1.44)	1.11*** (1.08-1.14)
	Women	1.50*** (1.35-1.66)	1.52*** (1.41-1.64)	1.16*** (1.12-1.21)

Below the odds ratio, 95% confidence interval (upper-lower) is shown. ***, P value <0.001.

Table 2: Odds ratio of CRP-stratified groups for MetS- associated conditions.

Discussion

In this study, we analyzed the medical checkup data with a focus on relationship between the serum CRP concentrations measured by an improved conventional CRP assay and other MetS-related parameters. Our multivariate logistic regression analysis showed that all the subject groups categorized based on CRP values (1 to 2, 2 to 3 and 3 to 9 mg/L) showed significant odds ratios (ORs) compared to the CRP<1 mg/L group. The median CRP values of this population (1.41 and 0.98 mg/L for men and women, respectively) was high compared with recent hs-CRP-based studies [8], and therefore, care should be taken when the absolute CRP values are compared with those of the hs-CRP-based studies. Nonetheless, in support of a cohort study performed in Japan [14], the association between CRP and the MetS criteria components is likely to be continuous down to the population with CRP levels near the median. Although

the present study suffers from the limitations stemming from the cross-sectional nature, such a population-based analysis based on an improved conventional CRP assay seems meaningful as such an assay is suitable to expanded populations, facilitating a percentile-based risk assessment, which seems important given that the true value is elusive with any of current CRP assays as we consider below.

CRP levels have been shown to associate with CVD development in originally healthy subjects, both in a cross-sectional study in general practice [15], and longitudinally in the US Physicians Health Study [16], the MONICA-Augsburg Cohort Study [17], and the MRFIT Study [18]. In the latter study, CRP levels predicted future cardiovascular events or CVD mortality. These and other observations have led to a consensus that minor elevations of CRP levels are a promising as a predictor of future vascular events. In our present study, CRP values between 1 to 2 mg/L showed significant ORs for BMI and hyperlipidemia, and notably also for the diabetic conditions and hypertension. To cite a few studies on eastern-Asian populations, a long-term prospective cohort study in Japan led to the authors to propose 1.0 mg/L hs-CRP as the cutoff point for high-risk for future development of coronary heart disease [14]. In the latter study, the median was 0.43 mg/L, consistent with the preceding studies in which Asian subjects had low hs-CRP levels compared to Western subjects [19,20]. A recent cohort study by Yoon et al. on a population of men with normal hs-CRP levels showed that, compared to the group with baseline CRP <0.2 mg/L, the group with 0.5 to 0.9 mg/L showed an OR of 1.79 for the new development of BMI >25 and an OR of 1.46 for that of low HDL-Chol <40 mg/dl [21]. In their unselected population, 4,132 among 14,522 subjects showed CRP values >1 mg/L, and this proportion was smaller than what we observed in the present study in which more than half of subjects showed values >1 mg/L. This difference could be due to the difference in the mean age (36.5 in Yoon et al., *vs.* 51 for the present study) and/or CRP measurement methods.

For quantification of low CRP concentrations, hs-CRP assays are considered to allow analysis of the range down to 0.3 mg/L. On the other hand, the three CRP levels proposed for risk assessment [22] were not that low: low risk (<1 mg/L); average risk (1~3 mg/L); and high risk (>3 mg/L). Recent guideline also recommended the use of hs-CRP >2 mg/L for decision of treatment of the subjects with an intermediate CVD risk score based on the family history of premature CVD, coronary artery calcium (CAC) score, and ankle-brachial index (ABI) [6]. This was based on the preceding reports including JUPITER trial that observed the lowest CVD event rate for the patients who reached hs-CRP <2.0 mg/L and LDL-Chol <2 mmol/L [23]. The recent CANTOS trial on IL-1β inhibition also used a subject categorization using 2 mg/L and showed that the inhibition improved CVD outcomes in subjects with hs-CRP higher than this cut point [24]. According to Roberts et al. [9] CV<10% appears to be the required imprecision level for clinical use. In Japan several improved conventional CRP methods that reach CV of 10% at 0.3 mg/L of CRP have been available [10]. The assay used in the present study had a minor difference from the one tested by Ishimine et al. and was likely to have CV <10% around 1 mg/L. Further, several manufacturers claim that they provide small POCT instruments for CRP quantification allowing measurement of low levels down to 0.5 mg/L with CV <10%. In Graca et al., a conventional CRP assay kit (CRPL3 Roche based on immunoturbidimetry) showed a CV of 7% at 1 mg/L [7] and displayed a satisfactory concordance with an hs-CRP assay from Roche. From these findings, we agree with Graca et al. that the new versions of conventional CRP assays can also be used in the context of CVD risk assessment.

For both hs-CRP and new conventional CRP assays, the calibration is generally not straightforward and, therefore, it seems premature to discuss the absolute value and cutoff point of CRP for decision making in treatments. Even for the hs-CRP methods that meet the FDA criteria, several studies reported strikingly large between-institute and between-reagent kit variances. Despite the similarity in the analyzed populations, the eight studies performed in Japan showed a wide spread of the median or mean of hs-CRP, for example, ranging from 0.10 to 0.60 mg/dL for men [8]. A specific example is Yamada et al. that used a nephelometry-based method (NA Latex CRP kit, Dade Behring Japan) and showed the median of 0.16 mg/L for 2,275 men. The median was 0.28 (men) and 0.20 mg/L (women) in Oda et al. based on a hs-CRP assay (N-latex CRP-2, Siemens Healthcare), but these were considerably lower than the corresponding values 0.60 and 0.30 mg/L found by the same authors in 2006 using the improved conventional assay (CRP-Latex II by Denka Seiken) [25]. Even after 2010, a worrisome discrepancy was found between Yamamoto et al. that showed the mean of 1.03 mg/L for men [26] and Otsuka et al. that showed the median of 0.3 mg/L for men [27]. In Roberts et al., nine hs-CRP methods showed the median value (of the 388 samples from blood donors) that ranged 0.78-1.14 mg/L, and the value at 75% percentile of the samples ranged 1.89-2.49 mg/L, indicating poor interchangeability between methods of independent manufacturers [28]. Overall, these findings call for substantial efforts on the standardization to reduce between-manufacturer and between-institution differences in hs-CRP assays and in conventional CRP assays as well.

Hs-CRP concentrations are routinely measured by nephelometric and turbidimetric immunoassays, in which comparison with a calibrant is crucial. The nine hs-CRP reagents kits examined in Roberts et al. showed different relative recoveries to different protein-based matrices, indicating the high sensitivity of these kits to matrix effects [28]. Importantly, Rzychon et al. found that lyophilization of plasma samples as well as the materials used for ERM-DA470k (that was supposed to succeed widely used ERM-DA470) causes dissociation into the monomeric form of CRP, which is normally a pentameric protein [29,30]. Such structural changes may hide some epitopes and affect the efficacy for agglutination by bridge formation between antibodies and antigens, affecting the degree of light-scattering. These observations led to the development of a new reference material (ERM-DA472) that is to be in the liquid frozen state [29]. A reference material for CRP has also been developed in Japan with no need for reconstitution [31]. However, besides the issue of the reference materials, subtle

differences in reagent kits, measurement instrument and sample handling may lead to unexpectedly large between-institutional differences in the hs-CRP values. It should also be noted a recent implementation of the microfluidic immunoassay enabled low-cost assay of the range reaching 0.2 mg/L [32]. A great number of researches on such methodologies distinct from immunoturbidimetry or nephelometry are underway [33]. Although the operational cost in clinics for such methods is not clear as yet, it is possible that many immunoturbidimetry- and nephelometry-based implementations may be eventually replaced with other methodologies including sandwich-assay formats.

To summarize the above, both hs-CRP and new conventional CRP assay have pitfalls, and at present which of them displays the true value is not clear [7]. Therefore, regardless of which of hs-CRP assays or new conventional CRP assays are used, the absolute CRP values (i.e, in mg/L) need to be carefully interpreted. Of note, compared to the absolute values, the relative values, i.e., the values represented by percentile were satisfactorily accurate for both approaches as shown in both Graca et al. and Roberts 2001. Together with practical merits (i.e., low cost and no need of special instruments), improved conventional CRP assays [10] may fit for the purpose of percentile value-based study. Together with the issue of limited dynamic range issue mentioned in Introduction, these considerations lead us to suggest that several improved conventional CRP assays that measure 1 mg/L CRP with a CV <10% may be suitable for population-based study on CRP. Considering all issues mentioned above, we surmise that it is beneficial to use conventional CRP assays hand-in-hand with hs-CRP assays and the assays based on new formats, such as microfluidic immunoassay. It is important to compare these assays whenever possible.

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***Corresponding author:** Reiko Seki, Department of Clinical Laboratory Science, Teikyo University School of Medical Technology, Japan, Tel: +81-3-3964-1211; Email: hyk@med.teikyo-u.ac.jp

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