

## Original Article

# Association between serum CRP concentrations with dietary intake in healthy and dyslipidaemic patients

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Serum CRP concentrations are elevated in subjects at risk of coronary events and in subjects with metabolic syndrome. Although dietary fat and antioxidants are known for their immune-modulating actions, their reported effects on CRP concentrations have been inconsistent. In the present study we have investigated whether dietary constituents are associated with serum CRP concentrations in healthy subjects and patients with dyslipidaemic. Dyslipidaemic subjects (n=238) were recruited from Hospital Outpatient Clinics in Guildford, UK. Apparently healthy subjects (n=188) were recruited from amongst adjacent University and Hospital employees. A validated food frequency questionnaire was used to estimate dietary intake. Dyslipidaemic patients had higher serum CRP [1.25 (0.42-3.26) mg/L] than control subjects [0.50 (0.17-1.42) mg/L] ( $p < 0.001$ ). In the dyslipidaemic patients, approximately 4% of the variation in serum CRP could be explained by dietary cholesterol intake ( $p = 0.015$ , 2.8%), and weakly by dietary vitamin C intake ( $p = 0.06$ , 1.2%). No relationship between dietary constituents and serum CRP concentrations was found among the healthy subjects. Hence the present study shows that serum CRP concentrations are increased in patients with classical coronary risk factors, and that they may be modulated by dietary cholesterol.

**Key Words:** CRP, dyslipidaemia, dietary intake, atherosclerosis, inflammation

## Introduction

C-reactive protein (CRP) is an acute phase reactant. It consists of five identical, non-glycosylated peptide subunits linked to form a cyclic polymer.<sup>1</sup> CRP immunoreactivity has been demonstrated in vulnerable and ruptured plaque.<sup>2</sup> The possible mechanisms for direct involvement of CRP in atherosclerosis and thrombosis include complement activation through binding to damaged cell membranes,<sup>3</sup> with subsequent induction of tissue factor production by monocytes.<sup>4</sup>

Elevated levels of CRP have been reported to be associated with increased risk of cardiovascular disease, myocardial infarction (MI), and coronary artery disease mortality among individuals with angina pectoris.<sup>5,6</sup>

There is substantial evidence that protein-calorie malnutrition and some specific nutrient deficiencies have adverse effects on the immune system. Alterations in the quality and quantity of dietary fat,<sup>7</sup> and abnormalities in lipid metabolism have been reported to influence immune responses.<sup>8</sup> Recent studies, both in vivo and in vitro have demonstrated that fatty acids can modulate immune responses.<sup>9,10</sup>

The results of studies investigating the association between serum CRP concentrations and dietary factors are controversial. We aimed to investigate whether the intake of the specific dietary constituents is associated with serum

CRP concentrations in healthy and dyslipidaemic subjects.

## Materials and methods

### Study design and subject selection

Two hundred and thirty-eight patients were recruited from the Outpatient clinics at the Royal Surrey County Hospital, Guildford, UK. One hundred and eighty-eight healthy subjects were employees at the University of Surrey or the Royal Surrey County Hospital, Guildford. Informed written consent was obtained from each subject, and ethics approval was obtained from the University of Surrey Advisory Committee on Ethics.

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Among the dyslipidaemic subjects, 82 were obese (BMI>30); 42 were diabetic (fasting plasma glucose>7mmol/L); 55 had established coronary heart disease (CHD), and 186 were hypertensive. Of the latter, 76 had a systolic blood pressure (SBP)  $\geq$  160 mmHg or a diastolic blood pressure (DBP)  $\geq$  100 mmHg. One hundred and seventy six patients were hypertriglyceridemic (serum triglycerides>1.8mmol/L) and 216 patients were hypercholesterolemic (serum total cholesterol > 5.2 mmol/L). Forty-two of the patients had a 10 year coronary risk >30% (calculated using the PROCAM algorithm), 54 had calculated 10 year risk of 20% to 30% and 142 patients had metabolic syndrome by NCEP-ATP III criteria.<sup>11</sup> In the comparison of CRP between patients and controls, 53 subjects were excluded from the control group because they were either obese (n=33), had metabolic syndrome (n=9) or were on medication (n=11).

#### ***Current dietary intake and estimation of antioxidants and fat***

Dietary intake over the previous 12 months was assessed for each subject by using a food frequency questionnaire (FFQ),<sup>12,13</sup> which was developed and validated against 7-day weighed records,<sup>14</sup> and biochemical markers of antioxidant status.<sup>15</sup> The short and long-term reproducibility of the FFQ has previously been reported.<sup>16</sup>

#### ***Anthropometric and other measurements***

All subjects were measured for height, waist and hip circumference (in centimeters) and weighed (in kilograms) using a stand-on Bio Impedance Analyzer (BIA) (Tanita-305 body fat analyzer, Tanita Corp., Tokyo, Japan). The latter was also used to estimate percent body fat. Body Mass Index (BMI) was calculated by the formula: BMI = weight (kg)/height (m<sup>2</sup>).

#### ***Physical Activity***

Physical activity levels were assessed using the James and Schofield human energy requirements equations.<sup>17</sup>

The energy cost of an activity by individual is calculated using physical activity ratio (PAR).

Physical activity levels can then be calculated as the total energy required for a twenty-four hour period (total energy expenditure TEE) as a ratio of the BMR over the twenty-four hour period.

The FFQ and physical activity questionnaire used for the present study were developed and used extensively by the Aberdeen University Department of Nutrition. The questions on physical activity based on the James and Schofield equations were selected from those used in the Scottish Heart Health Study (SHHS)/MONICA questionnaire.<sup>18</sup> Questions were divided into time spent on activities during work (including housework), during non-work time, and in bed (resting in bed and sleep). Questions were also included on time spent walking and cycling each day, and the number of times a week when the individual was physically active for at least twenty minutes during which time they became short of breath and sweated.

#### ***Blood Sampling***

Blood samples were collected between 8.30 and 10.30

a.m. after a 12-hour fast by venepuncture of the antecubital vein. Samples for lipid profile and high sensitivity C-reactive protein (hs-CRP) were taken into plain Vacutainer™ tubes and for glucose into fluoride-oxalate vacutainer™ tubes.

#### ***Materials***

All chemicals were obtained from Sigma (Sigma Chemical Co, Dorset, UK) unless stated otherwise.

#### ***Analytical Methods for Lipid Profiles, blood glucose and hs-CRP***

A fasting lipid profile, comprising total cholesterol, triglycerides and HDL-cholesterol, was determined for each patient. LDL-cholesterol was calculated using the Friedewald formula,<sup>19</sup> except for patients with serum triglycerides >4.0 mmol/L. Lipids, hs-CRP and glucose were measured by routine methods using a Bayer Advia 1650 analyzer (Bayer, Newbury, UK).

#### ***Statistical analysis***

Statistical analyses were carried out using the statistical package Minitab Release 13 (Minitab Inc., 3081 Enterprise Drive, State College, PA16081-3008, USA).

Analysis of covariance (ANCOVA) was used to assess differences after adjustment for important confounding factors such as age and physical activity. High-sensitivity CRP concentrations was found to be non-normally distributed and were therefore logarithmically transformed prior to parametric analysis. Stepwise multiple regression analysis was used to predict whether the hs-CRP concentrations were related to dietary antioxidants or fats. The following variables were entered into the equation to enable adjustment for potential confounding factors: obesity, metabolic syndrome or accumulating features of metabolic syndrome, diabetes mellitus, smoking, hypertriglyceridemia, blood pressure, established coronary heart disease, calculated 10 years coronary risk factors and drug treatment. A *p* value of <0.05 was considered significant.

## **Results**

#### ***Physical activity levels***

In healthy subjects, physical activity levels were positively associated with HDL cholesterol levels (*p*<0.01) and negatively associated with BMI (*p*<0.001) and waist/hip ratio (*p*<0.001). In the patient group, physical activity levels were positively associated with HDL cholesterol level (*p*<0.001) and negatively associated with BMI (*p*<0.001), serum triglycerides (*p*<0.001), diastolic blood pressure (*p*<0.01) and calculated 10-year coronary risk (*p*<0.05). No significant correlations between serum CRP levels and physical activity levels were observed in either patients or healthy subjects (*p*>0.05).

#### ***Smoking***

Among the 188 control subjects, 123 subjects had never smoked and 66 were current or ex-smokers. There were 32 current smokers and 34 ex-smokers. Although the median serum CRP concentrations were higher in both current smokers [1.00 (0.47-2.21)] and ex-smokers [0.94 (0.28-2.95)] compared with non-smokers [0.70 (0.17-2.14)]

**Table 1.** Comparison of dietary macro- and micronutrient intake between dyslipidaemic patients and control subjects

n	Patients 238	Control 135	p value
<b>Macronutrients</b>			
Proteins (g)	87.6 ± 1.9	80.9 ± 2.0	0.02
Total Fat (g)	76.8 ± 1.6	71.5 ± 2.0	0.04
CHO (g)	283 ± 8.6	277 ± 9.1	NS
Energy (MJ)	10.0 ± 0.3	10.2 ± 0.3	NS
Starch (g)	132 ± 4.1	111 ± 3.9	<0.001
Sugar (g)	145 ± 5.9	161 ± 7.2	NS
Fibre (g)	21.5 ± 0.7	18.7 ± 0.6	0.005
<b>Fat</b>			
Saturated fat (g)	29.4 ± 0.9	28.2 ± 0.6	NS
Monounsaturated fat (g)	27.7 ± 0.6	25.7 ± 0.8	0.04
Polyunsaturated fat (g)	10.6 ± 0.2	10.0 ± 0.3	NS
Cholesterol (mg)	410 ± 7.2	392 ± 9.0	NS
<b>Trace elements</b>			
Zinc (g)	10.5 ± 0.3	9.5 ± 0.3	0.01
Copper (g)	1.8 ± 0.1	1.7 ± 0.1	NS
Zinc/Copper ratio	6.4 ± 0.1	6.0 ± 0.1	0.04
Selenium (µg)	103.4 ± 3.8	89.9 ± 3.8	0.02
<b>Antioxidants</b>			
Vitamin E (mg)	6.5 ± 0.2	6.1 ± 0.2	NS
Vitamin C (mg)	42.5 ± 3.0	48.5 ± 4.2	NS
Carotene (µg)	2146 ± 79.0	2055 ± 85.3	NS
<b>Others</b>			
Fe (mg)	16.2 ± 0.5	15.4 ± 0.54	NS
Folate (µg)	288 ± 7.8	268 ± 7.7	NS
Mg (mg)	393 ± 11.7	388 ± 12.4	NS
Phosphorus (mg)	1629 ± 38.4	1600 ± 41.8	NS
K (mg)	4080 ± 848	4180 ± 1508	NS
Ca (mg)	1077 ± 28.2	1166 ± 33.1	0.04
Vitamin D (µg)	5.1 ± 0.2	4.3 ± 0.2	0.002

Values are expressed as Mean ± SEM. One-way ANOVA used for comparison between the patients and controls.

NS = Not significant

], this failed to reach statistical significance ( $p > 0.05$ ).

### Obesity

Among the 188 control subjects, 33 were obese, 58 were over weight, and 78 were of optimal weight. Obese subjects had significantly higher median serum CRP concentrations compared with over weight and optimal weight subjects ( $p < 0.001$ ). These results were shown to be statistically significant for male and female subgroups respectively and for the combined group ( $p < 0.001$ ).

### Serum hs-CRP concentrations in dyslipidaemic patients and healthy subjects

Serum CRP concentrations were significantly higher in the dyslipidaemic patients compared with controls for both male ( $p < 0.001$ ) and female ( $p < 0.01$ ) subgroups and for groups combined ( $p < 0.001$ ).

Serum CRP concentrations differed significantly between sub-categories with and without respectively; the presence of established CHD, metabolic syndrome, diabetes mellitus type 2, and obesity, and calculated 10-year coronary risk scores ( $p < 0.05$ ).

In an analysis of covariance the difference in serum CRP concentrations in dyslipidaemic patients compared with controls was no longer significant when BMI was used as a covariate ( $p > 0.05$ ).

### Serum CRP concentrations and CHD risk factors

In healthy subjects, serum CRP concentrations were positively associated with BMI ( $p < 0.001$ ), waist/hip ratio ( $p < 0.05$ ), serum triglycerides ( $p < 0.001$ ), serum total cholesterol ( $p < 0.01$ ) and systolic and diastolic blood pressure ( $p < 0.01$ ). In the patient group, serum CRP concentrations were positively associated with BMI ( $p < 0.001$ ), waist/hip ratio ( $p < 0.001$ ) and serum triglycerides ( $p < 0.001$ ).

**Table 2.** Multifactorial analyses of serum CRP concentrations

Confounders	Coefficient	R <sup>2</sup>	<i>p</i> %
Dyslipidaemia			
Obesity	+0.51	12.1	<0.001
Smoking	+0.28	3.8	0.004
Gender	-0.29	3.9	0.003
Dietary cholesterol	+0.001	2.8	0.01
Age	+0.01	1.6	0.04
Dietary vitamin C	1.01	1.2	0.06
Metabolic syndrome			
BMI	+0.2	9.4	0.002
Systolic blood pressure	-0.04	4.5	0.02
Dietary monounsaturated fat	+0.06	1.5	0.11

Using stepwise regression analysis

### ***Dietary intake of macro- and micronutrients in dyslipidaemic patients and controls***

The dyslipidaemic patients had a significantly higher dietary intake of protein ( $p < 0.05$ ) and total fat ( $p < 0.05$ ) compared with control subjects. No significant difference was observed for dietary intake of carbohydrate, sugar, and energy between patients and controls or between subgroups of patients, although the intake of starch was significantly higher among patients ( $p < 0.001$ ) (Table 1).

Dyslipidaemic patients had a significantly higher intake of monounsaturated fat ( $p < 0.05$ ) compared with control subjects. However there was no significant difference between controls and dyslipidaemic patients, or with patient subgroups, with respect to dietary intake of cholesterol, saturated fat, or polyunsaturated fat. Nor did the dietary intake of antioxidants differ significantly between the dyslipidaemic patients and control groups ( $p > 0.05$ ) (Table 1).

The dyslipidaemics had a higher intake of vitamin D ( $p = 0.002$ ) and lower intake of calcium ( $p = 0.04$ ) than controls.

### ***Multivariate analysis***

The best fitting models derived from stepwise multiple linear regression analysis showed that approximately 25.4% of the total variation in the serum CRP concentrations could be explained in the dyslipidaemic patients by obesity, smoking habit, gender, age and dietary cholesterol ( $p = 0.015$ , +2.8%), and Vitamin C ( $p > 0.05$ , -1.2%); approximately 15.4% of the total variation in serum CRP concentrations in the dyslipidaemic individuals with metabolic syndrome could be explained by body mass index, systolic blood pressure and dietary monounsaturated fat ( $p = 0.06$ , +1.5%) (Table 2).

No relationship between dietary constituents and serum CRP concentrations was found among the healthy subjects ( $p > 0.05$ ).

### **Discussion**

***Serum CRP concentrations are associated with traditional CHD risk factors in healthy individuals and patients with dyslipidaemia***

Several studies have previously shown a relationship between serum inflammatory markers such as CRP and CHD in cohort studies.<sup>20</sup> and this has been further supported by meta-analysis data.<sup>20</sup> Studies have reported that levels of serum CRP are related to individual coronary risk factors including the metabolic syndrome, as we have found in this study.<sup>20,21</sup>

Aronson *et al.*<sup>19</sup> reported a negative correlation between serum CRP concentrations and physical activity level. In our sample we found that the relationship between serum CRP concentrations and physical activity levels were of borderline significance, this may be mediated by an inverse relationship between activity and adiposity. We found a strong relationship between CRP and indices of adiposity in subjects with dyslipidaemia as previously reported for other groups of subjects.<sup>22</sup> Similar to previous studies.<sup>23</sup> We have found that serum CRP concentrations were elevated in overweight and obese subjects. Serum CRP concentrations had a closer correlation with BMI than with other coronary risk factors, including serum lipids, and systolic and diastolic blood pressure. It is possible that measures of BMI are less liable to intra individual variation compared to blood pressure, plasma glucose or serum lipids. It is known that adipose tissue secretes IL-6, a potent stimulant of hepatic CRP synthesis.<sup>24</sup>

We like Saito *et al.*<sup>25</sup> found a higher serum CRP concentration among smokers compared to non-smokers. There is good evidence that smoking induces oxidative and pro-inflammation stimuli.<sup>26</sup>

We found, as others have reported,<sup>27,28</sup> that CRP concentrations rose with increasing number of features of the metabolic syndrome, and the relative values were similar in our population to those reported in other Caucasian populations. These previous studies have also reported a positive association between serum CRP levels and fasting glucose, triglycerides and systolic blood pressure and a negative association with HDL cholesterol.<sup>27</sup> We found a significant positive association between serum CRP and triglycerides, total cholesterol and systolic and diastolic blood pressure, but the negative association with HDL cholesterol was non significant.

### **Serum CRP concentrations are associated with dietary constituents**

The effects of dietary factors on serum CRP concentrations are unclear. Soddon *et al.*<sup>29</sup> showed that high levels of serum antioxidant vitamin C and dietary fish intake were associated with lower serum CRP levels, whereas serum vitamin E, smoking and increased body mass index were associated with an increased serum CRP. Vitamin C is a water soluble antioxidant, with potentially beneficial effects in reducing oxidative tissue damage by chemical reduction of oxidant species.<sup>30</sup> Epidemiological data suggests that a high intake of vitamin C may protect against oxidative damage in vivo.<sup>31,32</sup> However, dietary vitamin C intake was only weakly related to serum CRP in our study. Fredrikson *et al.*<sup>33</sup> have reported no significant associations between CRP and dietary intake of total, saturated, monounsaturated, or polyunsaturated fat, fiber, vitamin E, or carotene. There was however, a weak inverse relationship between CRP and the intake of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and n-3 PUFA in the female subgroup. In their placebo-controlled, double-blind study, Geelen *et al.*<sup>34</sup> were unable to show an affect of fish oil on serum CRP concentrations and Mozaffarian *et al.*<sup>35</sup> could not find a relationship between dietary trans fatty acid and serum CRP concentrations. In our population sample we did not find a significant relationship between serum CRP concentrations and total, or specific dietary fats, apart from cholesterol.

### **Conclusions**

We have demonstrated that serum CRP concentrations are increased in patients with classical coronary risk factors that may be related to an enhanced state of immunoreactivation associated with these risk factors. Although we did not find a significant association between dietary constituents and serum CRP among healthy subjects, there was a weak relationship between dietary cholesterol intake and CRP in the dyslipidaemic patients. A clear limitation of our study is its cross-sectional design. It is not possible to be certain that the association between dietary constituents and CRP concentrations are causally-related. Furthermore, our study group was a small heterogeneous sample of dyslipidaemic patients, and it would be important to confirm these findings in a larger sample.

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## Original Article

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### 健康和血脂異常病人之血清 CRP 濃度與飲食攝取之相關

血清 CRP 濃度在有冠狀動脈疾病危險與有代謝症候群的人身上有升高之現象。雖然膳食脂肪及抗氧化劑已知具有免疫-調節功能，但對於 CRP 濃度的影響卻不一致。本研究我們研究健康者與血脂異常患者，其飲食成份是否與血清 CRP 濃度相關。血脂異常的研究對象(n=238)招募自英國 Guildford 醫院門診。明顯健康者(n=188)招募自相鄰的大學及醫院員工。採用經效度驗證的飲食頻率問卷評估研究對象的飲食攝取。血脂異常病人[1.25 (0.42-3.26) mg/L]比起對照組研究對象[0.50 (0.17-1.42) mg/L]有較高的 CRP 濃度( $p < 0.001$ )。血脂異常者其膽固醇攝取量可以解釋 4%的血清 CRP 變異( $p = 0.015$ , 2.8%)，飲食中維生素 C 攝取的解釋力則較弱( $p = 0.06$ , 1.2%)。在健康者中，並未發現飲食成份與血清 CRP 濃度有相關。因此，本研究顯示具有傳統冠狀動脈危險因子的病人，其血清 CRP 濃度較高，或許可以試著以膳食膽固醇來調整。

關鍵字：CRP、血脂異常、飲食攝取、動脈硬化、發炎。