Determinants of C-reactive protein concentration in blood

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C-reactive protein (CRP) is a very strong acute phase protein. During the acute phase of disease the CRP concentration can increase up to a thousand-fold. However, a higher CRP concentration is also observed during chronic stages of disease, for example in subjects with chronic bronchitis, periodontal disease or subjects with increased titers of *Helicobacter pylori* or *Chlamydia pneumoniae*. The concentration of CRP is also reported to be associated with age, sex, race, smoking, obesity, consumption of coffee and alcohol, stress, physical training, lipid levels, and blood pressure. Statins decrease the CRP concentration whereas estrogen increases it. With regard to most other drugs no consistent relationship has been reported.

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Regulation of C-reactive protein synthesis

C-reactive protein (CRP) is a very strong acute phase protein. In healthy, young subjects and resting situations the serum concentration is < 1.5 mg/l. In acute phase situations, however, the concentration can increase up to a thousand-fold. CRP is synthesized mainly in hepatocytes, but mRNA and CRP have been shown to be present in monocyte-derived macrophages in atherosclerotic plaques, lymphocytes and alveolar macrophages[1-4].

Different forms of CRP have been described. Firstly, the most common form is the cyclic, pentameric, blood-borne form termed "native" CRP which has activities mainly associated with the resolution of inflammation. Secondly there are conformationally altered and aggregated forms of CRP which display pro-inflammatory properties, and thirdly, there are proteolytically degraded forms of CRP which exhibit mixed activities[5]. *In vitro* studies on these different forms suggest that the heterogeneity has clinical relevance[5], but *in vivo* the levels of the different forms have not yet been studied.

There are substantial differences in the response of the acute phase proteins to stimuli. For example, serum amyloid A, another very strong acute phase protein, and CRP respond differently to stimuli such as surgical trauma or immunological tissue injury[6]. This suggests that independent, injury-specific pathways exist for the regulation of the synthesis of CRP and other acute phase proteins[6]. Since the clearance rate of CRP is not influenced by diseases such as rheumatoid arthritis, systemic lupus erythematosus, infections and neoplasia, it is expected that CRP concentrations are mainly determined by effects on the synthesis rate[7]. Differences in regulation have also been described for other acute phase proteins although most are regulated mainly by interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-α[8-10].

The variation of CRP concentrations in a healthy individual over time is rather large, but often it is possible to distinguish a stable basal level with a few outliers[11-13]. Peak values of CRP usually disappear within a few days of the inflammatory stimulus[14]. Seasonal variations in CRP concentrations have been described with higher concentrations in winter than in summer[15,16]. One study evaluated CRP levels in the morning and afternoon and found no difference, suggesting that there are no diurnal variations[12].

The concentration of IL-6 is usually strongly correlated with the concentration of CRP[17]. Weinhold et al.[18] reported that lipopolysaccharide injection in IL-6 knocked-out mice slightly increased the CRP concentration, while increases in CRP levels were much larger in IL-6+/+ mice. It has been suggested that IL-6 alone is not sufficient to induce an increase in CRP concentrations in mice, and additional factors, such as IL-1β, oncostatin M or leukemia inhibition factor,

are also required. In humans, the CRP concentration is weakly correlated with the concentrations of IL-1β and of TNF-α[17].

Demographic determinants of the C-reactive protein concentration (Table I)[15,16,19-49]

Many studies have reported a positive association between age and CRP concentration[19,20,42,50-58]. The extremes are clear when CRP concentrations in newborns (~0.1 mg/l)[59] are compared to those in subjects older than 85 years (CRP levels > 10 mg/l in 50% of cases)[60]. There are indications that the relationship between age and CRP is different for men and women, since in the MONICA study for the Augsburg samples there was a significant interaction between age and sex[20].

In women, CRP levels have been reported to be somewhat higher than in men[21,28,29]. It should be noted that fluctuations in CRP and cytokine concentrations have been reported during the menstrual cycle. This may cause problems when studying the effects of gen-

Table I. Factors associated with C-reactive protein concentration in blood.

Modulator	Effect	Population
Age	Positive	Middle-aged subjects from the general population[19-24], offspring of patients with MI[25], male survivors of MI[26]
	NS	Elderly men[27]
Sex	Higher in women	Children[28], middle-aged subjects from the general population[21], elderly[29]
	NS	Offspring of patients with MI[25]
Race	Higher in non-Hispanic black than in white	Subjects from the general population[30]
Smoking	Positive	Elderly men[27], middle-aged subjects from the general population[20,21,24,31], elderly[29], male survivors of MI[26]
	NS	Healthy, middle-aged subjects[22], middle-aged subjects from the general population[23], children[28], effect of smoking cessation[32]
Obesity (BMI)	Positive (explained ± 30% of variation of CRP)	Middle-aged subjects from the general population[20-24], children[28], offspring of patients with MI[25], elderly[29], healthy, middle-aged women[33]
Coffee consumption	Positive (expected)	Interaction with cytokines in hepatocytes[34]
Alcohol consumption	Negative (moderate)	Middle-aged subjects from the general population[20]
Seasonal variation	Winter peak	Persons over 75 years[15], healthy subjects[16]
	NS	Frohlich (insensitive assay)[35]
Psychological stress	NS	Healthy subjects[36]
Endurance training	Lowering of baseline increase	Healthy individuals[37]
		Healthy elderly subjects[38]
	"Acute" increase	16 hours after marathon[39]
Physical performance	Slightly negative	Elderly[40]
Lipids		
Total cholesterol	NS	Healthy, middle-aged women[22,33], middle-aged subjects from the general population[20,24]
Triglycerides	Positive*	Male survivors of MI[26], middle-aged subjects from the general population[24], patients with angina pectoris[41]
HDL-cholesterol	Negative*	Male survivors of MI[26], middle-aged subjects from the general population[24]
Blood pressure	Positive	Middle-aged subjects from the general population[20]
SBP	Positive	Male survivors of MI[21,23,26]
		Healthy, middle-aged women[33], middle-aged subjects from the general population[22]
DBP	Positive, but weaker than SBP	Middle-aged subjects from the general population[21], healthy, middle-aged women[33]
Insulin resistance/diabetes	Positive	Middle-aged subjects from the general population[23,42], male survivors of MI[26]
Periodontal disease	Positive	Random sample general population[43,44], patients with periodontitis vs healthy controls[45,46]
Helicobacter pylori	NS	Children[28], UAP patients[22,47]
Chlamydia pneumoniae	NS	UAP patients[47], middle-aged subjects from the general population[22,24]
		Dialysis patients[48]
	Positive	
Cytomegalovirus	NS	UAP patients[47], middle-aged subjects from the general population[22]
Total pathogen burden	Positive	Cardiovascular patients[49]
Chronic bronchitis	Positive	Middle-aged subjects from the general population[24]

BMI = body mass index; CRP = C-reactive protein; DBP = diastolic blood pressure; MI = myocardial infarction; NS = non significant; SBP = systolic blood pressure; UAP = unstable angina pectoris. * association present when adjusted only for age; disappeared when adjusted for age + BMI[33].

der[61,62]. Studies in transgenic CRP mice suggested that testosterone stimulates CRP expression because observed concentrations were higher in the males than in the females[63]. However, in humans a direct effect is not expected, since testosterone administration to transsexual ex-women did not increase the CRP concentration (Kooistra T., personal communication).

The CRP concentration is known to be higher in individuals who smoke[31,50,57,64-67]. However, the underlying mechanism is most likely an indirect consequence of the tissue-damaging effects of smoking and the smoker's increased susceptibility to respiratory infection. Because it will take some time for the tissue damage to disappear, it can be expected that the CRP concentration does not decrease after cessation of smoking, as indeed observed by Crook et al.[32].

Obesity is associated with an increased CRP concentration, presumably because adipose tissue is an important site of synthesis of IL-6 which is the main determinant of CRP gene expression[22,33,65,68,69].

The concentration of CRP is lower in case of intense physical activity or of regular physical exercise[37,40]. Notably, Schuit et al.[38] observed an increase in CRP concentrations in healthy elderly subjects who participated in a long-term exercise program. After severe exercise, for example running a marathon, the CRP concentration is increased because strenuous exercise induces an acute phase reaction[39]. This last observation may explain the discrepancy seen in the studies on regular physical exercise because the contrasting effects of exercise on insulin resistance may add up to any net effect, and the balance may depend on the subjects and the study design.

A relationship between blood pressure and the concentration of CRP has been reported[20]. This association is stronger for systolic than for diastolic blood pressure[21-23,26,33].

The concentration of CRP has also been correlated to that of lipids (e.g. triglycerides). A negative relationship with HDL cholesterol levels has been observed[26,41].

C-reactive protein and immunology

It is known that CRP is able to activate the complement cascade[70-73], and it has also been suggested that activated complement factors (e.g. C5a) are able to induce CRP synthesis[74].

Genetic factors affecting the C-reactive protein concentration

Recently, polymorphism in exon 2 of the CRP gene has been described, but no association with CRP concentration or regulation is known[75].

Since CRP is regulated by the cytokine concentration, genetic variations that influence the regulation of these cytokines may also be expected to affect the CRP concentration. For example, polymorphism in the promoter region of the IL-6 gene is associated with differences in the control of IL-6 expression[76]. It is expected that the increase in the levels of CRP after an acute phase stimulus is greater in individuals with the -174G allele than in those with the rare -174C allele. Polymorphism has also been described for other cytokines and again, it is expected to have an effect on the regulation of acute phase proteins, such as CRP. Offspring of patients with cardiovascular disease have higher CRP levels. This may be due to pleiotropic genetic effects, but it is also possible that genetic factors directly related to CRP contribute[25].

Dietary factors affecting the C-reactive protein concentration (Table I)[15,16,19-49]

Caffeine potentiates the induction of CRP by cytokines in human hepatoma cell lines[34]. It has not yet been studied whether caffeine exerts a similar effect *in vivo*.

Antioxidants, whether given in capsules or as dietary components, are expected to lower CRP concentrations because they lower the levels of oxidized LDL and thereby improve the inflammatory state. Indeed, in the VERA study[77], vitamin C and β-carotene lowered CRP levels but vitamin E had no effect. Devaraj and Jialal[78] administered α-tocopherol to healthy volunteers and to patients with type II diabetes. CRP levels were decreased in both groups. This study was not placebo-controlled, but after a wash-out period the concentration had increased to the pre-treatment values. In cross-sectional studies, no relationship was observed between intake of anti-inflammatory food supplements and the CRP concentration[17,29]. Consumption, by smoking volunteers, of green and black tea which are rich in flavenoids, had no effect on the concentration of CRP[17].

Consumption of fish oil has been suggested to lower plasma fibrinogen levels. This is not likely to occur through an effect on inflammation because CRP concentrations were not changed in healthy volunteers[79].

It would be expected that weight reduction would result in lower CRP concentrations because there will be less adipocytes, but no studies on the effect of diet for weight reduction on the CRP concentration have been published.

Subjects who report a moderate consumption of alcohol have a lower CRP concentration than those who claim no or high alcohol consumption[20]. Moderate alcohol consumption for 3 weeks results in a 35% reduction of the CRP concentration in healthy, middle-aged subjects (Sierksma A., personal communication).

Drugs affecting the C-reactive protein concentration (Table II)[17,52,78,80-96]

It is expected that anti-inflammatory drugs have an effect on the concentration of CRP. It has indeed been

Table II. Effects of drugs on C-reactive protein concentration.

Drug	Effect	Treated group	References
Lipid-lowering drugs			
Atorvastatin	Decrease	Stable angina pectoris	80
	Decrease	Hypercholesterolemic	81
Simvastatin	Decrease	Stable angina pectoris	80
	Decrease	Hypercholesterolemic	81,82
Pravastatin	Decrease	Survivors MI (CARE)	83
Acipimox	No effect	Hypercholesterolemic	82
Estrogen (oral contraceptives)	Increase	Young women	84-87
Estrogen (HRT)			
Estrogen	Increase	Healthy, postmenopausal women	52,88-90
	No effect	Postmenopausal women with CAD	91
Estrogen + progesterone	Increase	Healthy, postmenopausal women	52,88,89,92
Raloxifene	No effect	Healthy, postmenopausal women	90
Tamoxifen	Decrease	Healthy women	93
Antioxidants			
Tea	No effect	Healthy smokers	17
α-tocopherol	No effect	Healthy volunteers and patients with NIDDM	78
	Decrease	Patients with NIDDM	94
NSAID			
Aspirin	No effect	Healthy men	95
	Decrease	Patients with SAP	96

CAD = coronary artery disease; HRT = hormone replacement therapy; MI = myocardial infarction; NIDDM = non-insulin-dependent diabetes mellitus; NSAID = non-steroidal anti-inflammatory drugs; SAP = stable angina pectoris.

shown that non-steroidal anti-inflammatory drugs (NSAID), such as aspirin and ibuprofen, reduce oxidative stress[97]. No effect of aspirin on CRP was observed by Feng et al.[95] in healthy volunteers, but Ikonomidis et al.[96] observed a decrease of CRP in patients with stable angina pectoris who were treated for 6 weeks with 300 mg/day aspirin. These patients had higher CRP concentrations than healthy volunteers which suggests that aspirin treatment normalizes the increased CRP levels. It has not yet been published whether ibuprofen or other NSAID have an effect on the CRP concentration.

Aspirin also has a platelet-aggregation inhibiting effect and it has been suggested that CRP levels are lowered through this mechanism[98,99]. Against this hypothesis is the observation that ticlopidine, a platelet-aggregation inhibiting drug, has no effect on CRP levels in healthy volunteers and in patients with stable angina pectoris[100].

HMG-CoA reductase inhibitors have a favorable effect on cardiovascular risk, and this is partly due to their pleiotropic effects that are independent of those exerted on lipids. An effect on inflammation, and thus on CRP, has been suggested. Indeed, a decrease in CRP levels to normal basal concentrations is observed in patients who were treated with these drugs[82,83,87,101-103]. Fibrates, another type of lipid-lowering drug, have no effect on CRP although they decrease the plasma fibrinogen levels[104,105].

Drugs of another type that affect the CRP concentration are hormone-containing drugs. Several studies have reported an increase in CRP levels during hormone replacement therapy[52,88,92,106]. Even oral contraceptive use results in increased CRP levels[84-86].

C-reactive protein and chronic disease

The CRP concentration is associated with cardiovascular disease and with other inflammatory diseases, such as rheumatoid arthritis. Also, several components of the insulin-resistance syndrome, such as obesity and increased blood pressure, are associated with altered CRP values, a relationship we were the first to suggest in 1997[107] and which has since been confirmed by several other groups[22,33,87,108,109]. Also, patients with insulin-dependent diabetes mellitus have increased CRP levels[110,111].

Periodontal disease influences one's wellbeing. Indeed higher CRP concentrations have been observed in patients with periodontitis versus healthy controls[45,46]. Besides, in a random sample of the general population the periodontal health status was associated with the CRP concentration[43,44].

Increased titers of *Chlamydia pneumoniae*, *Helicobacter pylori* and *Cytomegalovirus* have also been suggested as the link between inflammation and cardiovascular disease. Indeed, Zhu et al.[49] observed an association between the total pathogen burden and the concentration of CRP in patients with cardiovascular disease. However, no association was observed between the titers of each of these pathogens and CRP[22,47]. It has been reported that the CRP concentration was lower in viral than in bacterial infections[112,113], but Heiskanen-Kosma and Korppi[114] could not confirm this in children with pneumonia of viral or bacterial origin.

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