Impact of Genetic and Environmental Factors on hsCRP Concentrations and Response to Therapeutic Agents

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BACKGROUND: Inflammation plays an instrumental role in all stages of atherosclerosis. High-sensitivity C-reactive protein (hsCRP), a systemic inflammatory marker, has been gaining recognition as an independent risk factor for cardiovascular disease (CVD). Both baseline hsCRP concentrations and drug-induced hsCRP changes are highly variable and potentially subject to genetic regulation.

CONTENT: This review summarizes the current studies examining the effect of genetic and environmental factors on baseline plasma hsCRP concentrations, with a main focus on C-reactive protein, pentraxin-related (CRP) genetic polymorphisms and various dietary components that affect hsCRP concentrations. We also address the association of CRP genetic variations with CVD risk, a relationship that may support or refute the causality of CRP in the atherosclerotic process. Moreover, we discuss the impact of CRP genetic polymorphisms on hsCRP changes in response to 3-week fenofibrate treatment in the genetic intervention of the Genetics of Lipid Lowering Drugs and Diet Network study.

SUMMARY: Genetic variants on the CRP locus and other loci and dietary and lifestyle factors are responsible for the interindividual variability of plasma hsCRP concentrations. CRP genetic variants further influence differing plasma hsCRP response after 3-week fenofibrate treatment in patients with metabolic syndrome. Future studies focusing on the influence and interaction of genetic variation on the hsCRP response to dietary and other behavior modification as well as drug treatment could have important implications for the development of more personalized preventive and therapeutic approaches to reduce CVD.

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C-reactive protein (CRP) is an acute-phase protein belonging to the family of proteins known as pentraxins. CRP is a plasma protein that is phylogenetically highly conserved across different species and participates in the systemic response to inflammation (1). CRP is synthesized and released primarily by hepatocytes, although reported data suggest local CRP synthesis and secretion may occur at other sites, such as macrophages (2) and smooth muscle cells (3).

Inflammation plays an instrumental role in all stages of atherosclerosis. A number of inflammatory markers have been investigated for use in predicting cardiovascular disease (CVD), and among these CRP has been gaining recognition as an independent risk factor for CVD events. Results of recent studies in animal models suggest that CRP also directly participates in the pathogenesis of CVD (4). In addition, increased high-sensitivity CRP (hsCRP) is associated with multiple risk factors for CVD, including obesity, insulin resistance, and hypertension, and has demonstrated significant predictive value for risk of metabolic syndrome (MetS) (5).

In apparently healthy individuals plasma hsCRP concentrations are widely distributed, reflecting substantial interindividual variability (6) driven by multiple environmental, sociodemographic, behavioral, and lifestyle factors, as well as obesity and type II diabetes (7, 8). Moreover, results of twin and family studies have led to estimations that genetic factors could contribute up to 35%–50% of the phenotypic variation of plasma hsCRP concentrations (9, 10).

This review summarizes results of studies that have examined the effects of genetic polymorphisms as

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2 Nonstandard abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; hsCRP, high sensitivity CRP; MetS, metabolic syndrome; SNP, single-nucleotide polymorphism; NHANES, National Health and Nutritional Examination Survey; TNF-α, tumor necrosis factor α; PUFA, polyunsaturated fatty acids; ALA, α-linolenic acid.
well as environmental factors, mainly dietary components, on plasma baseline hsCRP concentrations and associations with risk of CVD events. We also discuss the influence of C-reactive protein, pentraxin-related (CRP)\(^3\) genetic polymorphisms on individual differences in response to treatment with the lipid-lowering drug fenofibrate.

**Association between CRP Polymorphisms and Plasma Baseline hsCRP Concentrations and Risk of CVD Events**

Data from 3 cohorts, including the Women’s Health Study, the Pravastatin Inflammation/CRP Evaluation trial, and the Physicians’ Health Study, demonstrated that a set of CRP single-nucleotide polymorphisms (SNPs)—including 2 promoter SNPs, rs3093059 and rs3091244; intron 1 SNP, rs1417938; exon 2 SNP, rs1800947; and two 3′-UTR SNPs, rs1130864 and rs1205—was consistently associated with plasma hsCRP concentrations (11). Carson et al. evaluated 7 haplotype-tagging SNPs (including rs309358, rs3091244, rs1417938, rs1800947, rs3093066, rs1205, and rs2808630) in 6.8 kb surrounding the CRP locus and showed that CRP haplotypes were strongly associated with hsCRP concentrations in a large cohort study of CVD risk in European-American and African-American young adults. Among those SNPs, a promoter triallelic SNP rs3091244 was associated with the greatest proportion of overall hsCRP variance. Functional experiments revealed that this SNP resides within the hexameric core of transcription factor–binding elements. The presence of mutations alters a transcription factor (such as upstream stimulatory factor 1) binding motif and thus markedly affects the transcriptional activity of the CRP gene (12). Two haplotype constructs (tagged by the triallelic SNP rs3091244) displayed high interleukin (IL)-6–induced promoter activity, which was consistent with the observed strong association of those 2 haplotypes with hsCRP concentrations (13). The associations between CRP genotypes and plasma hsCRP concentrations were also observed in other large-scale studies, including the third National Health and Nutritional Examination Survey (NHANES III) and the Framingham Heart Study (14–17).

Although growing evidence from experimental studies supports the direct participation of CRP in the atherosclerotic process, its causality is still under debate. Genetic dissection of CRP may provide additional evidence determining its causal role by taking advantage of “mendelian randomization.” This method is similar to a randomized clinical trial in which the random assignment is the genotype that occurs at conception (18). So the observed association between a disease and functional genetic polymorphisms is not susceptible to residual confounding or reverse causation, which may potentially bias the results of observational studies (18). The hypothesis is that if CRP is causally involved in disease pathogenesis, then alleles that influence CRP synthesis could mediate the onset of clinical CVD events. In this regard, multiple cohort studies have examined the effect of CRP SNPs associated with baseline hsCRP concentrations on atherosclerotic disease progression or occurrence of clinical CVD events (such as myocardial infarction). Results from the Cardiovascular Health Study in older American adults, with a median follow-up of 13 years, showed that SNP rs1417938 was associated with increased risk of stroke and CVD mortality in white participants and SNP rs3093058 was associated with a 4-fold increased risk of myocardial infarction in black participants, whereas 2 SNPs (rs1800947 and rs1205) were associated with decreased risk of CVD mortality in white participants (17). The direction of the CVD risk estimates paralleled that of the associations with plasma hsCRP concentrations. The NHANES III investigators also reported that the triallelic SNP rs3091244 was cross-sectionally associated with the prevalence of coronary heart disease (CHD) in the non-Hispanic white population (15). These results have been controversial, however, because results from other cohorts, including those of the Physicians’ Health Study, the Framingham Heart Study, and the Rotterdam Study, suggested little or no association between CRP genotype and risk of myocardial infarction or stroke (11, 16, 19). Interpretation of these results requires consideration of a number of factors. First, the CRP locus accounts for only a small proportion of the variability of hsCRP concentrations. Therefore, some studies may be underpowered for detection of the genetic impact on disease outcome, especially given the small sample size and relatively small relative risk of disease. Second, age may play an important role, because positive associations are more commonly seen among older than among younger individuals (17). Third, the influence of CRP may vary in association with disease stage. The association between CRP genotype and clinical CVD, together with the absence of association with carotid intima-media thickness (20), which measures the extent of subclinical atherosclerotic disease, suggests a

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\(^3\) Human genes: CRP, C-reactive protein, pentraxin-related; IL6, interleukin 6 (interferon, beta 2); TNF, tumor necrosis factor (TNF superfamily, member 2); IL1B, interleukin 1, beta; TH, tyrosine hydroxylase; ADRB1, adrenergic, beta-1, receptor; ADRB2, adrenergic, beta-2, receptor; APOD, apolipoprotein D; ESRP, leptin receptor; IL6R, interleukin 6 receptor; GCKR, glucokinase (hexokinase 4) regulator; HNF1A, HNF1 homebox A.
greater involvement of CRP in the transition from subclinical to clinical disease than in atherosclerosis progression. This observation was in agreement with the lack of association between plasma hsCRP concentrations and carotid intima-media thickness (21). Moreover, associations are more likely observed in cases of disease with fatal outcomes (11, 17, 19), which is in line with the involvement of hsCRP concentrations in the increase of infarct size (22), suggesting the possibility that through an effect on acute-phase response (23), CRP genotype may be more strongly associated with more severe events. Finally, the use of genetic markers as an instrumental variable to assess causality could lead to misleading conclusions in the presence of linkage disequilibrium, genetic heterogeneity, pleiotropy, or population stratification (24).

In summary, current studies have provided convincing evidence of the significant impact of CRP polymorphisms on baseline plasma hsCRP concentrations; however, the genetic association with risk of CVD events is equivocal despite the fact that hsCRP concentrations are a strong independent predictor of CVD. In this regard, the recently launched international consortium, the CRP CHD Genetics Collaboration, from more than 30 relevant studies of CRP genetic variants and CHD risk, should provide compelling evidence to elucidate the casual relationship of CRP genetic variants and circulating hsCRP concentrations with CHD (25).

**CRP Polymorphisms Affect hsCRP Response to Fenofibrate Lipid-Lowering Therapy**

Fenofibrate, a PPAR (peroxisome proliferator-activated receptor) α agonist, is a member of the fibrate class of lipid-lowering drugs. Both experimental studies and clinical trials have demonstrated that fibrates may additionally reduce CVD risk through antiinflammatory effects, including attenuation of constitutive and induced CRP gene expression (26, 27). Fibrates target both the atherogenic “lipid triad” (high triglycerides and low HDL with small and dense LDL particles) and inflammation (28). Because both phenotypes are important components of diabetes and MetS and potentially link these 2 metabolic disorders to CVD (29, 30), fibrates are hypothesized to be candidates for treating dyslipidemia associated with diabetes and MetS, and more effective in reducing CVD in those at high risk (31–33).

It has been documented that the individual response to fibrate is highly variable, and multiple genes have been identified to be associated with the efficacy of lipid lowering (34, 35). However, the genetic impact on the antiinflammatory effect of this drug is less well understood. In this regard, we examined the association of CRP genetic polymorphisms with hsCRP response to a 3-week fenofibrate treatment among US white participants in the Genetics of Lipid Lowering Drugs and Diet Network study, a single-arm, uncontrolled, nonrandomized intervention funded by the National Heart, Lung, and Blood Institute with the purpose of identifying genetic variants associated with interindividual variability of triglyceride responses to a high fat meal and fenofibrate (36, 37). The study population consisted of 539 men and 584 women, and the majority of participants were reenrolled from the ongoing National Heart, Lung, and Blood Institute Family Heart Study conducted in 2 genetically homogeneous centers (Minneapolis and Salt Lake City) with predominantly white populations. The baseline characteristics of the study participants are provided in Supplemental Table 1, which accompanies the online version of this review at http://www.clinchem.org/content/vol55/issue2. In this study, and consistent with previous reports, SNPs m301G>A>T (rs3091244), i178T>A (rs1417938), 3u1273C>T (rs1130864), and 3u2131C>T (rs1205) were significantly associated with baseline hsCRP concentrations. Moreover, we observed effects of the m301G>A>T and the i178T>A SNPs on hsCRP response to fenofibrate intervention among participants with MetS. Specifically, G-allele carriers for the m301G>A>T SNP displayed greater reduction of hsCRP concentrations than noncarriers. Similarly, TT individuals with the i178T>A SNP had greater reductions in hsCRP concentrations than TA and AA individuals (Fig. 1). It is of interest that the alleles associated with high baseline inflammatory status appear to be more resistant to the antiinflammatory effect of fenofibrate. Conversely, in the presence of an inflammatory stimuli, these alleles, such as the minor allele of 3u1273C>T (previously reported as 1444C>T, rs1130864, in complete linkage disequilibrium with i178T>A, rs1417938), have been shown to be associated with greater hsCRP increases in patients undergoing coronary artery bypass graft or periodontal therapy (14, 38). The mechanism underlying the modulation of genetic variants on hsCRP response to fenofibrate among individuals with MetS is undefined. However, because both SNPs appear to be involved in transcription factor–binding motifs, it is possible that some of the genetic effects may be attributable to the interaction of these transcription factors, in particular upstream stimulatory factor 1 with PPARα. Our findings have practical relevance because lipid-lowering drugs, such as statins and fibrates, remain critical elements in the prevention of CVD (35). In addition, although a series of large-scale intervention trials using fibrates have established the role of fibrates in normalizing lipid profiles, the results regarding the efficacy of fibrates in the reduction of CVD
events have been inconsistent (39). Further subgroup analyses revealed that features of the MetS modify the effect of fibrates on CVD such that cardiovascular benefits are largely confined to individuals with features of the MetS (39). Our data provide additional insight into the heterogeneity of the treatment response, suggesting that genetic differences could further differentiate individual responses to fenofibrate and thus potentially may affect the disease outcome among individuals at high risk. Last, if the reduction of hsCRP concentrations may require different lifestyle modifications or therapeutic regimens.

**Association of Plasma hsCRP Concentrations with Other Inflammatory Markers and Genetic Determinants**

CRP is considered an important downstream inflammatory marker, and its activity may reflect the action of several upstream cytokines. Experimental studies indicated that hepatic expression of CRP is regulated at the transcription level by various cytokines, including IL-6, IL-1β (1), and tumor necrosis factor α (TNF-α) (41). A recent study revealed that the protein kinase C pathway is also involved in the regulation of CRP, and that IL-8 acts as a potential physiological protein kinase C activator that significantly induces hepatic CRP release (42). CRP may also exert proinflammatory activity through the induction of adhesion-molecule expression, activation of the complement system, and inhibition of fibrinolysis by inducing plasminogen activator inhibitor-1 (43, 44). Because of the strong biological connection between CRP and those inflammatory mediators, circulating hsCRP values correlate closely with other markers of inflammation such as IL-6, TNF-α, intercellular adhesion molecule-1, and fibrinogen (45–47). Some of those inflammatory markers have been shown to predict CVD; however, the association is less significant and consistent than that of hsCRP (47). Nevertheless, characterizing the relationship between hsCRP and other markers of inflammation opens up a new perspective for the identification of improved predictors and additional therapeutic targets for CVD.

Understanding of the interrelation between CRP and other inflammatory mediators has laid the foundation for the search for the genetic determinants of CRP that reside outside of the CRP locus. To date, multiple candidate genes involving the CRP regulatory pathway have been reported to affect hsCRP concentrations. The interleukin 6 (interferon, beta 2) (IL6) –174G/C and –572C/G SNPs, the tumor necrosis factor (TNF superfamily, member 2) (TNF) G-308A SNP, and the interleukin 1, beta (IL1B) –511C/T and 3954C/T SNPs have all been shown to be associated with baseline hsCRP concentrations (48–50). In addition to the obvious inflammation candidate genes, other loci reported to be associated with hsCRP concentrations include tyrosine hydroxylase (TH), a rate-limiting enzyme of catecholamine biosynthesis that has been linked to CRP production; 2 β-adrenergic receptors, adrenergic, beta-1-, receptor (ADRB1) and adrenergic, beta-2-, receptor (ADRB2) (51); and the apolipoprotein E (APOE) locus (52).

In addition, a genome-wide association study among 6345 healthy women participating in the Women’s Genome Health Study, in which 336 108 SNPs were successfully genotyped, has revealed several novel loci associated with plasma hsCRP concentrations. Those new loci included leptin receptor (LEPR), interleukin 6 receptor (IL6R), glucokinase (hexokinase 4) regulator (GCKR), and the hepatic transcription-factor gene HNF1 homeobox A (HNF1A). Because these genes are directly involved in MetS, insulin resistance, β-cell function, and weight homeostasis, this new pathogenetic link opens a new field involving the regulation of plasma hsCRP and the roles of CRP in CVD.

![Fig. 1. Plasma hsCRP response to 3-week fenofibrate treatment among patients with MetS according to CRP ](i178T>A and m301G>A>T genotypes (geometric means ±95% CI).)](h11550.png)

P-value obtained from additive model was adjusted for baseline hsCRP concentrations, change of triglyceride, change of IL-6, age, sex, body-mass index, smoking status, alcohol intake, physical activity and use of aspirin and nonsteroidal antiinflammatory drugs; drugs for lowering cholesterol, diabetes, and hypertension; and hormone treatment in women. Patients with hsCRP >10 mg/L at the baseline or after the treatment were excluded from the analysis.
as both a useful biomarker and an active participant (53).

**The Association of Environmental Factors with Plasma hsCRP Concentrations**

The environmental factors discussed below have been shown to contribute to the phenotypic variation in hsCRP. Dietary intake has been among the best studied (7, 8).

**DIETARY FAT AND hsCRP CONCENTRATIONS**

Epidemiological studies have revealed that dietary fatty acid composition can modulate inflammation (54). A cross-sectional study of 730 women from the Nurses’ Health Study I cohort found that women in the highest quintile of trans fat intake had a 73% higher hsCRP concentration compared with those with the lowest quintile of intake (55). Similarly, data from both a subsample of the Health Professionals Follow-up Study (n = 446 men) and the NHANES participants (1999–2000, n = 4900) suggested that high fat intake, particularly saturated and trans fatty acids, was associated with increased hsCRP concentrations (56, 57). Intervention trials have provided further evidence in support of the relationship of increases in inflammation with the intake of saturated and trans fatty acids. Pirro et al. found that the 8-week consumption of a low cholesterol/low saturated fat diet significantly decreased hsCRP concentrations in 35 hypercholesterolemic patients (58). Similar increases were reported in healthy individuals when trans fatty acid was used as a replacement fat within the context of a high-fat diet (39% fat) (59).

The relationship between dietary n-3 polyunsaturated fatty acids (PUFAs) [α-linolenic acid (ALA), eicosapentaenoic acid, and docosahexaenoic acid] and chronic inflammation has also been examined. The Nurses’ Health Study I cohort (n = 727 women) showed lower concentrations of markers of inflammation and endothelial activation, including hsCRP, IL-6, and E-selectin, among women in the highest quintile of n-3 PUFA compared with those in the lowest quintile (60). Moreover, results from a study of 3042 Greek healthy adults showed that study participants who consumed at least 300 g of fish per week had 33% lower hsCRP compared with those who did not consume fish (61). Several clinical trials also confirmed the anti-inflammatory effect of ALA. Rallidis et al. found a significant reduction of hsCRP and IL-6 concentrations after ALA supplementation, whereas LA supplementation decreased cholesterol concentrations with no significant effects on inflammation in 90 male dyslipidemic patients (The ratio of n-6 to n-3 was 1.3:1 in the ALA-supplemented group and 13.2:1 in the LA-supplemented group) (62). In addition, Bemelmans et al. reported a lowering of hsCRP concentrations in 103 moderately hypercholesterolemic men and women after consumption of an ALA-enriched margarine compared to those consuming an LA-enriched margarine (63). Although epidemiological studies have shown an inverse correlation between consumption of dietary fish or fish oil (eicosapentaenoic acid and docosahexaenoic acid) and biomarkers of inflammation (60, 64), results from clinical trials are inconclusive (65, 66).

As for monounsaturated fatty acids, results of a cross-sectional study of a Japanese population consisting of 1556 men and 1461 women suggested that intake of oleic acid was inversely associated with hsCRP concentrations (67). Another study of 180 patients with MetS, but free of CVD, demonstrated that patients consuming a Mediterranean-style diet high in oleic acid as well as fiber and antioxidants had lower serum concentrations of hsCRP and cytokines (IL-6, IL-7, and IL-18) compared with a control group consuming their usual diet (68).

Taken together, the current evidence supports the notion that the overall quantity of fat intake; the sources and type of dietary fat, with special emphasis on saturated and trans fatty acids, ALA and oleic acid; and the ratio of n-6 to n-3 PUFA play significant roles in modulating hsCRP concentrations and other markers of inflammation.

**CARBOHYDRATES, DIETARY FIBER, MICRONUTRIENTS, AND hsCRP CONCENTRATIONS**

The quantity and quality of carbohydrate intake affect the risk of CVD through alteration of blood lipid concentrations and inflammation. High intake of refined carbohydrates, such as starch and sugar, results in the increase of postprandial hyperglycemia, which may lead to the increased circulating concentrations of free radicals, proinflammatory cytokines, and hsCRP (69). Among 18 137 healthy women participating in the Women’s Health Study, dietary glycemic index and glycemic load were significantly associated with hsCRP; the highest quintiles of glycemic index and glycemic load were associated with high hsCRP compared with the lowest quintiles (70).

Regarding the relation between dietary fiber and inflammation, data from the NHANES indicated that dietary fiber intake was inversely associated with serum hsCRP concentration among 3920 adult participants (71). Moreover, a longitudinal study involving 524 individuals demonstrated that the likelihood of increased hsCRP concentrations was 63% lower (odds ratio 0.37, 95% CI 0.16, 0.87) in participants in the highest quartile of total fiber intake compared to participants in the lowest quartile (72). The antiinflammatory effect of
dietary fiber may be mediated through reduction of lipid oxidation, normalization of bowel flora, and inhibition of hyperglycemia (73).

The antiinflammatory effects of micronutrients (i.e., vitamins and minerals) have also been explored, and several studies have demonstrated an inverse association between vitamin E, vitamin B6, carotenoids, and magnesium and plasma hsCRP concentrations (74).

FRUIT, VEGETABLE, AND NUT INTAKE AND INFLAMMATION
Esmaillzadeh et al. reported that in 486 Tehran women, higher intakes of fruits and vegetables were associated with a lower risk of MetS and lower hsCRP concentrations, and after adjustment for age, body-mass index, and waist circumference, mean plasma hsCRP concentrations across increasing quintile categories of fruit intake was 1.94, 1.79, 1.65, 1.61, and 1.56 mg/L and of vegetable intakes were 2.03, 1.82, 1.58, 1.52, and 1.47 mg/L (75). In a randomized controlled 4-week trial in 64 nonsmoking men, study participants who consumed 8 servings per day of carotenoid-rich vegetables and fruit had significantly reduced hsCRP concentrations compared with those who consumed 2 servings per day (76). The antiinflammatory effect appears to be mainly attributable to the antioxidant components of fruits and vegetables (77).

High consumption of nuts that are rich in mono-unsaturated fatty acids, PUFA, and arginine has been inversely associated with risk of CVD. The beneficial effect is partially attributable to an antiinflammatory effect (78).

DIETARY PATTERNS AND hsCRP CONCENTRATIONS
In addition to focusing on individual nutrients and food items, research has also focused on dietary patterns, which may reveal more details of nutrient–nutrient synergy and interaction with respect to the modulation of inflammation.

Results of a cross-sectional study of 732 healthy women suggested that a prudent dietary pattern characterized by higher intakes of fruit, vegetables, legumes, fish, poultry, and whole grains was inversely associated with plasma hsCRP, whereas a Western-type diet characterized by high intakes of red and processed meats, sweets, desserts, french fries, and refined grains was positively associated with hsCRP. Study participants categorized as having the most prudent diet had average hsCRP of 1.3 mg/L compared with an average of 1.7 mg/L in those classified as having the most Western diet (55). Interestingly, a randomized trial conducted among 180 patients with MetS found that patients who consumed the Mediterranean diet rich in fruits and vegetables, nuts (274 g/day), whole grains (103 g/day), and olive oil (8 g/day) for 2 years showed significantly reduced inflammatory markers such as hsCRP, increased insulin sensitivity, and decreased risk of MetS compared with patients following a prudent diet (68).

OTHER LIFESTYLE FACTORS AND hsCRP CONCENTRATIONS
Results from a prospective study of 27 055 healthy women participating in the Women’s Health Study clearly demonstrated that the beneficial effects of physical activity on a reduced risk of CVD could be mediated in part by decreases in chronic inflammation in addition to other known risk factors (79). The inverse association between high levels of physical activity or exercise training and markers of chronic inflammation such as hsCRP has been consistently reported (80–82). Physical activity and cardiorespiratory fitness have been estimated to reduce hsCRP concentrations by 6%–35% (83). For example, data from the NHANES III, which included 13 748 participants, demonstrated that the odds ratios for increased hsCRP concentrations were 0.98 (95% CI 0.78–1.23), 0.85 (0.70–1.02), and 0.53 (0.40–0.71) for participants who engaged in light, moderate, and vigorous physical activity, respectively, compared with participants who did not engage in any leisure-time physical activity (80). Moreover, physically active individuals displayed low concentrations of lipopolysaccharide-stimulated production of IL-6, IL-1β, TNF-α, TLR4, and hsCRP compared with inactive subjects (81). Moreover, intervention in the form of a 12-week aerobic and resistance exercise regimen significantly reduced hsCRP concentrations among physically inactive young and old adults down to the similar values observed among physically active young and old adults (82). In addition to effects observed in healthy individuals, the exercise training also significantly improved hsCRP among patients with chronic diseases, such as CHD and type II diabetes (84, 85).

Increasing levels of physical activity appear to reduce plasma hsCRP by mechanisms beyond effects on body weight, as evidenced by a study showing that both low levels of physical activity and high levels of body-mass index were independently associated with increased inflammatory markers (86). Physical activity has been postulated to have favorable effects on proatherogenic adipokines, insulin metabolism, and endothelial function (87). Other mechanisms have also been suggested, including exercise-induced release of heat-shock protein, alteration of immune function, or reduced tissue hypoxia (88).

Whereas physical inactivity as a CVD risk factor is not yet well understood, cigarette smoking is a well-established risk factor. Smoking triggers an immunologic response and vascular injury, which are associated.
with increased concentrations of inflammatory markers, such as hsCRP (89). Several studies have demonstrated strong links between smoking and increased concentrations of hsCRP and other markers of inflammation (90, 91). For example, a study in 2920 British older men showed that compared with never smokers, current cigarette smokers had significantly higher concentrations of hsCRP (2.53 vs 1.35 mg/L). However, most inflammatory levels improved within 5 years of smoking cessation, but reversion to values of never smokers did not occur until more than 20 years of smoking cessation (91). Data from the NHANES III with 15,489 participants (1988–1994) suggested that after adjustment for traditional CVD risk factors, cigarette smoking was related to increased concentrations of hsCRP and fibrinogen, with a dose-dependent and temporal relationship (89).

Collectively, dietary habits and other lifestyle factors that influence hsCRP provide the tools for CVD risk prevention. Furthermore, preventive and therapeutic recommendations could be even more successful if they were tailored by using genetic information aimed at the CRP gene. Current knowledge is not solid enough, however, to use this approach to provide clinically relevant advice.

Conclusions

The CRP locus, together with other loci that are involved in its regulatory pathway, significantly influences plasma hsCRP concentrations. The reported impact of CRP genetic variants on CVD risk and events provides some support to the notion that CRP may play a causal role in the pathogenesis of atherosclerotic disease. The evidence for this role is not yet conclusive, however. Moreover, CRP genetic variants could affect hsCRP response to lipid-lowering drugs, such as fenofibrate, and thus may have a defining influence on the success of the intervention. Environmental exposures such as diet and other lifestyle factors also affect interindividual variation of hsCRP phenotypes, and there is support for the interaction of genetic and environmental factors in these complex traits. Therefore, further characterization of the influence and interaction of genetic variation on the hsCRP response to dietary and other behavior modification as well as drug treatment could have great implications for the development of more personalized preventive and therapeutic approaches to CVD.

References

C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet 2005;77:64–71.


