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# Human C-reactive protein and the metabolic syndrome

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## Abstract

**Purpose of review—**Low-grade inflammation is characteristic of the metabolic syndrome (MetS). C-reactive protein (CRP), the best characterized biomarker of inflammation, is also an independent predictor of future cardiovascular events. The purpose of this review is to outline the role of inflammation and high sensitivity CRP in the MetS.

**Recent findings—**Emerging laboratory and epidemiological data now link inflammation and high sensitivity CRP to insulin resistance and adiposity and other features of MetS. Furthermore, in large prospective studies, increased high sensitivity CRP levels in MetS confer greater cardiovascular risk. CRP has been shown to impair insulin signaling and contributes to atherothrombosis.

**Summary—**Thus, although a high CRP level predisposes to increased cardiovascular risk in MetS, future investigation is warranted on the in-vivo role of CRP in mediating vascular effects and resulting in increased cardiovascular events in MetS patients.

### Keywords

C-reactive protein; inflammation; metabolic syndrome; vascular cells

## Introduction

Metabolic syndrome (MetS) comprises a cluster of abnormalities with insulin resistance and adiposity as central features [1–3]. Five diagnostic criteria have been identified by the ATPIII, and the presence of any three features [central obesity, dyslipidemia (high triglycerides, low HDL), hypertension, and impaired fasting glucose (IFG)] is considered sufficient to diagnose the syndrome [4]. Twenty-four percent of the US adults have the MetS, and the prevalence increases with age (44% at age of 60 years) [5].

## The metabolic syndrome and cardiovascular disease

Patients with MetS have an increased burden of cardiovascular disease (CVD) [6–8]. In the Kuopio Ischemic Heart Disease study, Lakka *et al.* [6] convincingly showed that men with the MetS, even in the absence of baseline coronary artery disease (CAD) or diabetes, had a significantly increased mortality from CAD. In the Botnia Study, the MetS was defined as the presence of at least two of the following risk factors: obesity, hypertension, dyslipidemia, or microalbuminuria. Cardiovascular mortality was assessed in 3606 patients with a median follow-up of 6.9 years. In women and men, respectively, the MetS was seen in 10 and 15% of patients with normal glucose tolerance (NGT), 42 and 64% of those with

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IFG/impaired glucose tolerance (IGT), and 78 and 84% of those with type 2 diabetes mellitus (T2DM). The risk for coronary heart disease (CHD) and stroke was increased three-fold in patients with MetS ($P$ <0.001), and cardiovascular mortality was increased six-fold (12.0 versus 2.2%, $P$ <0.001) [6–8]. Using data from Third National Health and Nutrition Examination Survey (NHANES III), Alexander *et al.* [7] also reported that the MetS is very common, with 44% of the US population over 50 years of age meeting the ATPIII criteria. Those with MetS without diabetes had higher CHD prevalence (13.9%), and those with both MetS and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither. MetS was a significant univariate predictor of prevalent CHD. The Hoorn Study examined 615 men and 749 women aged 50–75 years, without diabetes or a history of CVD at baseline and reported that the National Cholesterol Education Program (NCEP)-ATPIII definition of MetS was associated with about a two-fold increase in age-adjusted risk of fatal CVD in men and nonfatal CVD in women [6–8]. The lower but significant risks were also obtained using the WHO, American College of Endocrinology (ACE), and European Group on Insulin Resistance (EGIR) definitions of MetS. Also, Ford [5] using the modified NCEP-ATPIII criteria on the NHANES cohort, also reported significantly increased prevalence of MetS in the US population.

## The metabolic syndrome and diabetes

Apart from the effect on cardiovascular morbidity and mortality, the components of the MetS have been associated with diabetes. Factor analysis was used to identify the components of the MetS on 1918 Pima Indians [9]. Insulin resistance factor was strongly associated with diabetes in a 4-year follow-up. Also, the body size and the lipid factor predicted diabetes, whereas the blood pressure (BP) factor did not.

In the West of Scotland Coronary Prevention Study (WOSCOPS) [10], MetS increased the risk for CHD event and for diabetes. MetS continued to predict CHD events in a multivariate model incorporating conventional risk factors. Patients with four or five features of the syndrome had a 3.7-fold increase in risk for CHD and a 24.5-fold increased risk for diabetes compared with those with none. The Prospective Cardiovascular Münster (PROCAM) study [11] also reported a 2.3-fold increased incidence of CVD in patients with the MetS, and these effects persisted after adjustment for conventional risk factors.

Thus, overall MetS, *per se*, confers an increased propensity to both diabetes and CVD. Although individual components of MetS independently contribute to increased cardiovascular risk, in concert, they do not explain the increased propensity of vascular disease in patients with MetS, and the precise mechanisms for this increased propensity remain to be elucidated. Inflammation is pivotal in all phases of atherosclerosis from foam cell formation to culmination in acute coronary syndromes. Also, several lines of evidence demonstrate that diabetes is a proinflammatory state. It appears that low-grade chronic inflammation is a central feature of MetS and could contribute to increased risks of both CVD and diabetes in MetS.

## Inflammation, high sensitivity C-reactive protein, and increased cardiovascular risk in metabolic syndrome

Circulating levels of several inflammatory biomarkers have been studied to assess their value in predicting CVD. The best characterized and well standardized biomarker of inflammation is C-reactive protein (CRP). Numerous studies [12] have now confirmed that CRP levels are elevated in patients with the MetS. Furthermore, it has been proposed that high sensitivity CRP (hsCRP) be added as a clinical criterion for MetS and for creation of an hsCRP-modified CHD risk score [12].

Evidence supporting the hypothesis that elevated CRP levels contributes to increased cardiovascular risk is now available from at least six major prospective studies, these include the Physicians' Health Study (PHS), Women's Health Study (WHS), Atherosclerosis Risk in Communities (ARIC), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) in the United States and Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) and Reykjavik studies from Europe [13–18]. Additionally, with regards to MetS, Yudkin *et al.* [19] in 107 nondiabetic patients conducted *Z*-score analyses and found a very significant correlation between inflammatory markers and several features of the MetS. CRP levels were shown to be strongly associated with insulin resistance calculated from the homeostatic model assessment (HOMA) model, BP, low HDL, triglycerides, and to levels of the proinflammatory cytokines, IL-6 and tumor necrosis factor (TNF). BMI and insulin resistance were the strongest determinants of the inflammatory state. There is a linear relationship between the number of metabolic features and increasing levels of hsCRP. Furthermore, Festa *et al.* [20] in the Insulin Resistance and Atherosclerosis Study (IRAS) showed that hsCRP was positively correlated with BMI, waist circumference, BP, triglycerides, cholesterol, LDL cholesterol, plasma glucose, and fasting insulin, and inversely correlated with HDL cholesterol and insulin sensitivity index. The strongest associations are observed between CRP levels, central adiposity, and insulin resistance. The largest study to date that examined the association between inflammation and the MetS was the NHANES III study [21]. In a representative sample of the US population (8570 participants >20 years of age), patients with the MetS, defined using ATPIII criteria, were more likely than those without the syndrome to have elevated levels of markers of inflammation such as CRP, fibrinogen as well as leukocyte count. Thus, there appears to be a clear relationship between the numbers of metabolic features and increasing hsCRP levels. In addition, we have shown that CRP levels were equivalent to the ratio of high-molecular weight (HMW) adiponectin:CRP in predicting MetS using receiver operating characteristic (ROC) analyses [22•]. Furthermore, Sugiura *et al.* [23] have also reported that leptin (positively) and adiponectin (negatively) were independently associated with CRP. It is also worthwhile noting that adiponectin decreased CRP synthesis and secretion, whereas leptin increases CRP secretion. Thus, MetS is a proinflammatory state characterized by increased CRP levels.

Ridker *et al.* [24] evaluated in a large-scale population cohort of the WHS, the potential interrelationships between CRP, the MetS, and incident cardiovascular events (CVEs). In the 8-year prospective follow-up of 14 719 women in the WHS, an hsCRP of more than 3 mg/l in patients with MetS predicted a greater age-adjusted relative risk (RR) for future CVE. Furthermore, they reported that at all levels of severity of the MetS, CRP added prognostic information with regard to subsequent risk of incident CVE and was additive to the Framingham risk score. Thus, it has been proposed that hsCRP be added as a clinical criterion for MetS and for creation of an hsCRP-modified CHD risk score [25].

In the WOSCOPS, in which 6447 men were followed for 4.9 years, an hsCRP level of more than 3 mg/l predicted greater cardiovascular risk in patients with the MetS in a multivariate model [26]. In the Framingham Offspring Study [13], both CRP and MetS were independent predictors of new CVEs but were not additive. In an Italian study, patients with MetS and CRP of more than 3 mg/l had higher incidence of both carotid and CAD. Pischon *et al.* [27] showed in the Nurses' Health Study and Health Professionals Follow-up Study that although MetS was a strong predictor of CHD in both men and women, however, CRP was additive in men only. It should be emphasized that in this study, a modified definition of MetS was used, as waist circumference, BP, and glucose were not available at baseline. In a smaller Japanese Study [28] of 461 patients with acute myocardial infarction (AMI), CRP levels were additive to MetS in predicting future major adverse cardiac events (MACEs). Furthermore, recent investigation relating increased CRP levels and MetS in 1044 older

(≥65 years of age) individuals has also led to the conclusion that MetS is associated with low-grade systemic inflammation, and the association is mainly supported by a strong independent correlation between waist circumference and high hsCRP levels. Collectively, all these studies support the hypothesis that an increased CRP in the setting of MetS confers an increased risk of future CVEs.

Additionally, a genome-wide association study [24] has been performed recently among 6345 apparently healthy women in which 336 108 single-nucleotide polymorphisms (SNPs) were evaluated as potential determinants of plasma CRP concentration. Overall, seven loci that associate with plasma CRP at levels achieving genome-wide statistical significance were found. Two of these loci [glucokinase hexokinase 4 regulator (GCKR) and hepatic nuclear factor 1 homeobox A (HNF1A)] are suspected or known to be associated with maturity-onset diabetes of the young, one is a gene-desert region on 12q23.2, and the remaining four loci are in or near the leptin receptor protein gene, the apolipoprotein E gene, the IL-6 receptor protein gene, or the *CRP* gene itself. The protein products of six of these seven loci are directly involved in MetS, insulin resistance, β cell function, weight homeostasis, and/or premature atherothrombosis. Thus, it is concluded that a common variation in several genes involved in metabolic and inflammatory regulation have significant effects on CRP levels, consistent with CRP's identification as a useful biomarker of risk for incident vascular disease and diabetes. All these findings have sparked increased discussion about the formal addition of hsCRP to the criteria of MetS. In addition to the prognostic information that hsCRP evaluation might add to the current definition of MetS, there are several other practical appeals of hsCRP measurement. First, hsCRP is strongly associated with components of MetS that are difficult to measure in routine clinical practice, such as impaired fibrinolysis and insulin resistance [19,20]. Also, the widespread availability of commercial assays now for hsCRP has made its measurement simple and inexpensive. In addition, hsCRP does not display diurnal variation and demonstrates long-term stability comparable with cholesterol, and it can be reliably evaluated with a single nonfasting measurement [29,30]. The addition of hsCRP measurement to our present diagnosis of the MetS may significantly improve the early detection of risk for future diabetes and CVE in individuals. Overall, it appears that in patients with MetS, an elevated CRP confers a greater risk for CVE by its action on vascular cells such as activation of monocytes and induction of endothelial cell dysfunction.

## C-reactive protein, the metabolic syndrome, and type 2 diabetes mellitus

The MetS is a constellation of risk factors that predispose to increased cardiovascular risk and morbidity and is a common disorder affecting 35% of the US adults based on data from the NHANES III [31]. MetS confers an increased propensity to diabetes and CVD. All of these characteristics are also associated with elevated levels of CRP. Among participants without diabetes in the WHS, high CRP levels and BMI were the only independent correlates of fasting insulin level modeled as a continuous dependent variable. After adjustment for BMI and other risk factors for diabetes, the RR for elevated fasting insulin (≥51.6 pmol/l) increased with tertile of hsCRP [32]. Also, in the WHS, the addition of hsCRP to the traditional definition of the MetS provided the best predictive algorithm. A similar pattern of results was observed in the WOSCOPS [26], which followed 6447 middle-aged men for 5 years. hsCRP, coded as at least 3 mg/l versus less than 3 mg/l, was strongly predictive of incident CHD after stratification by MetS status. Among men in the 'low-CRP/metabolic syndrome absent', 'high-CRP/metabolic syndrome absent', 'low-CRP/metabolic syndrome present', and 'high-CRP/metabolic syndrome present' groups, the RRs for incident CHD were 1.0 (referent), 1.6 [95% confidence interval (CI), 1.3–2.1], 1.6 (95% CI, 1.2–2.1), and 2.75 (95% CI, 2.1–3.6), respectively. With regards to diabetes, numerous groups have demonstrated that diabetes is a proinflammatory state as evidenced by increased

levels of circulating CRP. However, it is not clear whether the increased CRP in diabetes is a causative factor in inducing inflammation and complications of diabetes.

## C-reactive protein and development of diabetes

Elevated hsCRP levels have also been implicated in the development of T2DM, a powerful risk factor for CVD. Prospective studies [5,8,12,20,33–36] have found strong, graded relations between hsCRP and incident diabetes, which in many instances persisted after adjustment for BMI and other covariates. In the WHS, women in the top quartile of the hsCRP distribution were more than four times as likely to develop diabetes than were women in the bottom quartile during 4 years of follow-up and this was also reported by Festa *et al.* [20] in the IRAS study population. The IRAS found a linear increase in mean log hsCRP values according to the number of metabolic disorders present in each of 1008 patients without diabetes or CAD. Also, in the Nurses' Health study, hsCRP was a strong predictor of development of diabetes. This has been confirmed now by at least 10 prospective studies. These observations suggest that CRP is expressed in advance of overt diabetes and may be an integral component of prediabetic insulin resistance.

## C-reactive protein and insulin signaling

Two recent reports provide provocative evidence that CRP may impair insulin signaling [37,38]. Xu *et al.* [37] show that recombinant CRP attenuates insulin signaling through the regulation of spleen tyrosine kinase (Syk) on small G-protein ρA, jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK), insulin receptor substrate-1 (IRS-1), and endothelial nitric oxide synthase (eNOS) in vascular endothelial cells. Recombinant CRP suppressed insulin-induced nitric oxide production, inhibited the phosphorylation of Akt and eNOS, and stimulated the phosphorylation of IRS-1 at the Ser307 site in a dose-dependent manner. These events were blocked by treatment with an inhibitor of ρA-dependent kinase Y27632, or an inhibitor of JNK SP600125, or the transfection of dominant negative ρA cDNA. Also, antibody to CD32 partially blocked the recombinant CRP-induced phosphorylation of JNK and IRS-1 and restored, to a certain extent, the insulin-stimulated phosphorylation of Akt. D'Alessandris *et al.* [38] determined the effects of human recombinant CRP (hrCRP) on insulin signaling involved in glucose transport in L6 myotubes. Their data suggest that hrCRP may cause insulin resistance by increasing IRS-1 phosphorylation at Ser307 and Ser612 via JNK and extracellular signal-regulated kinases 1 and 2 (ERK1/2), respectively, leading to impaired insulin-stimulated glucose uptake, glucose transporter 4 (GLUT4) translocation, and glycogen synthesis mediated by the IRS-1/phosphoinositide-3 kinase (PI-3K)/Akt/glycogen synthase kinase 3 (GSK-3) pathway.

Thus, these provocative evidences of CRP levels being associated with increased CVE and diabetes confirm evidence from numerous laboratories delineating the effects of CRP on atherothrombosis *in vivo* and *in vitro* as reviewed previously [39]. Also, a recent study [40••] examined the intravascular kinetics of CRP and its relationship to features of MetS. The production rate of CRP that mirrored plasma CRP levels was shown to be significantly correlated to features of MetS such as waist, high triglycerides, low HDL, and also to biomarkers of inflammation and adipose tissue biology such as high IL-6 and low adiponectin. Furthermore, CRP is also synthesized in the adipose tissue [41] and may be present in excessive quantities in patients with abdominal obesity, eventually resulting in insulin resistance and diabetes.

## Experimental evidence linking C-reactive protein to its effects on vascular cells

CRP exerts proatherogenic effects on vascular cells such as endothelial cells, smooth muscle cells, and monocyte–macrophages.

### C-reactive protein, endothelial dysfunction, and metabolic syndrome

Endothelial dysfunction is now recognized to play a critical role in the initiation and progression of atherosclerotic vascular disease [42–44]. Furthermore, endothelial function assessment by brachial flow-mediated dilatation is a surrogate marker of cardiovascular risk [45,46] and has been shown to be decreased in MetS [47–52]. It is well established that the individual components of the MetS are related to endothelial dysfunction. Previous studies [53,54] have shown that obesity, low HDL cholesterol, IGT, hypertriglyceridemia, and hypertension are associated with decreased endothelium-dependent vasodilatation. Also, insulin resistance is associated with endothelial dysfunction [55,56].

An impressive amount of data now implicates CRP in inducing endothelial cell activation and dysfunction *in vitro* as well as *in vivo* [57–61]. Several observations demonstrated that CRP levels correlated inversely with endothelial vasoreactivity *in vivo* [62,63]. The most compelling data implicating CRP as a determinant of endothelial dysfunction were studies [64,65] demonstrating that human CRP reduced basal and stimulated nitric oxide release from arterial and venous endothelial cells. Our group has explored various mechanistic events involved in CRP-mediated eNOS inhibition and documented that increased NADPH oxidase activation and guanosine triphosphate cyclohydrolase 1 (GTPCH1) downregulation are associated with CRP-mediated eNOS uncoupling in human aortic endothelial cells (HAECs) *in vitro* [66•]. In-vivo studies [57,58,60–63] have shown that CRP impairs endothelial vasoreactivity and decreases eNOS activity. Guan *et al.* [67••] showed that a single intravenous (i.v.) injection of adeno-associated virus (AAV) vector with CRP (AAV–hsCRP) to male rats resulted in efficient and sustained expression of CRP in the liver and other tissues and an increase in serum CRP to 15 μg/ml at 2 and 4 months. This was associated with an increase in systolic and mean arterial pressure. Also, the authors go on to show impaired endothelium-dependent vasoreactivity in the AAV–hsCRP versus AAV–green fluorescent protein (GFP) administered control rats. Previously, we have shown [59] that CRP inhibits prostacyclin synthase resulting in decreased prostacyclin, a potent vasodilator. Thus, CRP, by inducing endothelial dysfunction, could put patients with MetS at further risk for hypertension.

Patients with MetS are in a procoagulant state as evidenced by increased circulating plasminogen activator inhibitor-1 (PAI-1). We have shown that CRP induces PAI-1 and decreases tissue plasminogen activator (tPA) in endothelial cells [68,69]. CRP appears to induce PAI-1 antigen and activity via upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activities [70].

### C-reactive protein, monocytes—macrophages, and metabolic syndrome

The proinflammatory effects of CRP that have been documented in monocyte–macrophages include induction of tissue factor, proinflammatory cytokines, ROS, chemokine receptor 2 (CCR2), matrix metalloproteinases (MMPs) release, CD11b expression, and oxidized LDL uptake as well as inhibition of cholesterol efflux and lipopolysaccharide (LPS)-induced IL-10 release [71–77,78•]. Another important in-vivo demonstration made recently is from our group on the induction of myeloperoxidase (MPO) activity in macrophages by CRP administration [79].

Several lines of experimental evidence support monocyte chemotactic protein-1's (MCP-1) role in atherogenesis, insulin resistance, and adipose tissue-mediated inflammation. Also, CRP has been reported to induce MCP-1 in endothelial cells and its receptor, CCR2 on monocytes [73]. Furthermore, Esposito *et al.* [80] have reported that in both obese and nonobese women, IL-10 levels were significantly lower in women with MetS. In this regard, we have reported that CRP inhibits LPS-induced IL-10 release from human monocytes-derived macrophages (HMDM) [81].

Oxidative stress, mainly superoxide, plays a critical role in the pathogenesis of MetS parameters [82]. Fortuño *et al.* [83] have reported increased mononuclear cell (MNC) activation in MetS compared with controls. They also demonstrate increased superoxide, nitrotyrosine and oxidized LDL in MetS compared with controls, although MetS patients studied in this report were on various medications including statins (39%) as well as oral hyperglycemics (21%). Thus, there is an emergent need to study monocyte biology in drugnaïve MetS patients that has not been explored yet. Furthermore, CRP has been shown by numerous investigators including our group to result in increased superoxide production as a result of enhanced NADPH oxidase activity in endothelial cells as well as in human peripheral blood monocytes [59,66•,72,78•,82]. Also, in-situ hybridization revealed the presence of CRP mRNA that colocalized with p22phox, an essential component of NADPH oxidase [84]. We also demonstrated in Wistar rats that CRP stimulates superoxide production in macrophages via upregulation of NADPH oxidase [72].

Increased oxidized LDL in the vessel wall and circulation has been shown in patients with acute coronary syndrome and was associated with endothelial dysfunction and predicted CVE [85]. Furthermore, patients with MetS exhibit increased plasma oxidized LDL levels [86]. In addition, we recently showed that CRP promotes oxidized LDL uptake and cholesterol ester accumulation in Wistar rats [78•].

Patients with MetS are in a procoagulant state. Tissue factor is increased in morbidly obese persons with abnormal glucose tolerance compared with those with NGT [87]. Diamant *et al.* [87] also demonstrated increased tissue factor-containing microparticles in T2DM that correlated significantly with features of MetS in this population. *In vivo*, several lines of evidence indicate that CRP promotes procoagulant activity [39]. We have shown that CRP promotes tissue factor activity *in vitro* and *in vivo* in the rat model, and that it is via activation of ROS and NF-κB [72]. Very importantly, recent results from the justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER) trial, especially in those patients with hsCRP more than 2 mg/l but no other risk factors ($n$ = 6375), showed a significant reduction in CVE with rosuvastatin supporting that CRP appears to be an active participant in atherothrombosis [88••].

NF-κB is a pivotal transcription factor involved in the induction of specific proinflammatory genes [89]. Studies in animal models have demonstrated the importance of I-κ-B kinase b (IKKb) in the pathogenesis of insulin resistance in obese and diabetic rodents. Recently, it has also been shown in humans that obesity is associated with an increase in NF-κB binding in the nucleus and a decrease in the inhibitory κB in the MNC, with increased mRNA for TNF [90], IL-6, macrophage inhibitory factor (MIF), and MMP-9, consistent with the proinflammatory state. Recently, we have shown that CRP induces NF-κB activity in rat macrophages *in vivo* [72,78•].

All these reports support the notion that CRP is an effector molecule able to induce a proatherogenic phenotype. Therapeutic lifestyle change is the cornerstone of therapy in patients with MetS. Weight loss and caloric restriction appear to decrease CRP levels and the inflammatory burden in MetS. Other strategies that have been employed to decrease the

inflammatory burden in MetS include the use of statin therapy and thiazolidenediones. In patients with MetS, we have previously shown that in addition to LDL lowering, simvastatin therapy compared with placebo resulted in decreased hsCRP levels and NF-κB activity in MNCs, thereby decreasing the resulting inflammatory state of MetS [91].

## Conclusion

Emerging laboratory and clinical evidences have provided strong relationship between CRP and various features of MetS. The addition of CRP to the present definition of the MetS may help identify patients at high risk for future diabetes and CVD. Further investigation is clearly needed not only to clarify the molecular role of CRP in the pathogenesis of MetS but also in shedding new light on to the role of CRP specifically in mediating vascular effects and conferring CVE in MetS patients with high CRP levels.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 245).

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