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Role of C-Reactive Protein in Contributing to Increased Cardiovascular Risk in Metabolic Syndrome

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Abstract Metabolic syndrome is associated with increased propensity for diabetes and cardiovascular disease. Low-grade inflammation is characteristic of metabolic syndrome. C-reactive protein, the best characterized biomarker of inflammation, is also an independent predictor of future cardiovascular events. This review outlines the role of high-sensitivity C-reactive protein in contributing to increased cardiovascular risk in metabolic syndrome by inducing endothelial cell dysfunction and activating monocytes.

Keywords CRP · Metabolic syndrome · Inflammation · Cardiovascular risk

Introduction

Metabolic syndrome (MetS) comprises a cluster of abnormalities, with insulin resistance and adiposity as central features [1–3]. Five diagnostic criteria for MetS have been identified by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), and the presence of any of these three features—central obesity, dyslipidemia (high triglycerides, low high-density lipoprotein [HDL] cholesterol), hypertension, and impaired fasting glucose—is considered sufficient to diagnose the syndrome [4]. About 24% of US adults have MetS, and the prevalence increases with age (44% at age 60 years) [5].

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Metabolic Syndrome and Cardiovascular Disease

Individuals 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 MetS, even in the absence of baseline coronary artery disease (CAD) or diabetes, had a significantly increased mortality from CAD. In the Botnia study, 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 3,606 individuals, with a median follow-up of 6.9 years. In women and men, respectively, MetS was seen in 10% and 15% of participants with normal glucose tolerance, 42% and 64% of those with impaired fasting glucose/impaired glucose tolerance, and 78% and 84% of those with type 2 diabetes mellitus. In individuals with MetS, the risk for coronary heart disease (CHD) and stroke was increased threefold ($P<0.001$) and the risk for cardiovascular mortality was increased sixfold (12.0% vs 2.2%; $P<0.001$) [6–8]. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Alexander et al. [7] reported that MetS is very common, with 44% of the US population over 50 years of age meeting the NCEP-ATP III criteria. Individuals 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 to 75 years without diabetes or a

history of CVD at baseline and reported that the NCEP-ATP III definition of MetS was associated with about a twofold 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 World Health Organization, American College of Endocrinology, and European Group on Insulin Resistance definitions of MetS. Ford [5,] using the modified NCEP-ATP III criteria on the NHANES cohort, also reported significantly increased prevalence of MetS in the US population.

Metabolic Syndrome and Diabetes

Besides the effect on cardiovascular morbidity and mortality, the components of MetS have been associated with diabetes. Hanson et al. [9] used factor analysis to identify the components of MetS on 1918 Native Americans of the Pima tribe. 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 factor did not.

In the West of Scotland Coronary Prevention Study (WOSCOPS), MetS increased the risk for CHD events and diabetes [10]. MetS continued to predict CHD events in a multivariate model incorporating conventional risk factors. Participants with four or five features of the syndrome had a 3.7-fold increase in risk for CHD and a 24.5-fold increase in risk for diabetes compared with those with no features of the syndrome. The Prospective Cardiovascular Münster (PROCAM) study [11] also reported a 2.3-fold increased incidence of CVD in participants with MetS, and these effects persisted after adjustment for conventional risk factors.

Overall, MetS 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 individuals 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. 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

Evidence supporting the hypothesis that elevated C-reactive protein (CRP) levels contribute to increased cardiovascular risk is now available from at least six major prospective studies [12]. These are the Physician's Health Study (PHS) [13], Women's Healthy Study (WHS) [14], Atherosclerosis Risk in Communities (ARIC) study [15], and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [16] in the United States and the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg (MONICA/KORA Augsburg) [17] and the Age Gene/Environment Susceptibility (AGES)-Reykjavik [18] studies in Europe. The largest of the American cohorts is the WHS, a prospective evaluation of 27,939 initially healthy American women who underwent high-sensitivity CRP (hsCRP) evaluation along with a full lipid panel and Framingham risk assessment and were monitored over a period of 8.3 years for the occurrence of first-ever cardiovascular events. Overall, baseline hsCRP levels in the WHS were a strong predictor of future vascular events; the relative risks for those with lowest to highest quintiles of hsCRP at baseline were 1.0, 1.8, 2.3, 3.2, and 4.5 ($P<$ 0.001). After adjustment for age, smoking, diabetes, blood pressure, and hormone replacement therapy, the risk in the top quintile of hsCRP was 2.3 (95% CI, 1.6–3.4). A combined approach, using both a lipid panel and hsCRP, provided improved prediction of cardiovascular event–free survival. Most importantly, hsCRP levels remained a highly significant predictor of risk in the WHS after adjustment for the Framingham Risk Score. Data on hsCRP from the PHS and WHS have been corroborated by similar analyses from other large cohorts from the United States and Europe. In a case-cohort analysis of 12,819 apparently healthy middle-aged men and women participating in the ARIC study over a 6-year follow-up period, the relative risks of incident CHD for those with baseline hsCRP levels less than 1.0, 1.0 to 3.0, and greater than 3.0 mg/L were 1.0, 1.6, and 2.5, respectively, after adjusting for age, gender, and ethnicity [15]. Almost identical data were derived from a prospective evaluation of 3435 German men participating in the MONICA/KORA Augsburg Cohort Study, in which 191 incident coronary events occurred during 6.6 years of follow-up [17]. In this study of men, as in the WHS study of women, hsCRP levels at baseline were independently associated with incident coronary events. These effects remained significant ($P < 0.001$) after adjustment for Framingham Risk Score. The Reykjavik Study included 2,459 incident events during an 18-year follow-up period [18]. Although this prospective study used an hsCRP cut-point for relative risk of 2.0 rather than 3.0, and thus would tend to underestimate effects compared with other cohorts, a highly significant fully adjusted odds ratio of 1.5 was observed. Within the AFCAPS/TexCAPS analysis of 5,742 apparently healthy individuals enrolled in a randomized primary prevention trial of lovastatin versus placebo, each quartile increase in baseline hsCRP was associated with a 21% increase in the risk of a first cardiovascular event

(95% CI, 4–41%), an effect that again persisted after control for all individual components of the Framingham Risk Score [16]. Similarly, in an analysis of 1,666 individuals free of CVD enrolled in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, hsCRP levels correlated modestly with 10-year Framingham Risk Scores yet showed minimal relation to any individual component of the score itself.

Inflammation, High-Sensitivity C-Reactive Protein, and Increased Cardiovascular Risk in Metabolic Syndrome

Numerous studies have now confirmed that CRP levels are elevated in individuals with MetS [12]. Furthermore, it has been proposed that hsCRP be added as a clinical criterion for MetS and for creation of an hsCRP-modified CHD risk score [12].

With regard to MetS, Yudkin et al. [19], conducted Z-score analyses in a study 107 nondiabetic individuals 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, blood pressure, low HDL, and triglycerides, and also to levels of the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF). Body mass index 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 body mass index, waist circumference, blood pressure, triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, plasma glucose, and fasting insulin, and that it was inversely correlated with HDL cholesterol and the insulin sensitivity index. The strongest associations were observed between CRP levels, central adiposity, and insulin resistance. The largest study to date that examined the association between inflammation and MetS was NHANES III [21]. In a representative sample of the US population (8570 participants > 20 years of age), individuals with MetS, defined using NCEP-ATP III criteria, were more likely than those without the syndrome to have elevated levels of markers of inflammation such as CRP, fibrinogen, and leukocyte count.

Ridker et al. [12, 14] evaluated inter-relationships between CRP, MetS, and incident cardiovascular events among 14,719 apparently healthy women who were followed for an 8-year period for myocardial infarction, stroke, coronary revascularization, or cardiovascular death; 24% of the cohort had MetS at study entry. At baseline, median CRP levels for those with zero, one, two, three, four, or five characteristics of the metabolic syndrome were 0.68, 1.09, 1.93, 3.01, 3.88, and 5.75 mg/L, respectively (P for trend < 0.0001). Over the 8-year follow-up, cardiovascular event-free survival rates based on CRP levels above or below 3.0 mg/L were similar to survival rates based on having three or more characteristics of MetS. At all levels of severity of MetS, CRP added prognostic information on subsequent risk. Additive effects for CRP were also observed for those with four or five characteristics of MetS. Thus, in this study, those who had hsCRP levels of less than 3 mg/L without MetS had the best cardiovascular survival, whereas those who had hsCRP levels greater than 3 mg/L with MetS had the worst cardiovascular survival.

An almost identical additive interaction between hsCRP, MetS, and subsequent vascular risk was observed in WOSCOPS, a randomized intervention trial of pravastatin that monitored 6447 middle-aged men over a 5-year period. In WOSCOPS, hsCRP greater than 3 mg/L at baseline was highly predictive of incident vascular events after stratification by the presence or absence of MetS [22]. Specifically, the observed relative risks of future coronary events in the low-CRP/MetS-absent, high-CRP/MetS-absent, low-CRP/MetS-present, and high-CRP/MetS-present subgroups within WOSCOPS were 1.0 (referent), 1.6, 1.6, and 2.8, respectively ($P<0.05$).

Smaller but consistent effects were observed in the Cardiovascular Health Study. Suzuki et al. [23] studied 4,017 men and women ≥ 65 years of age without baseline congestive heart failure (CHF) or diabetes participating in the Cardiovascular Health Study, an observational study with 12.2 years follow-up and 966 cases of incident CHF. Baseline CRP/MetS or IL-6/MetS were defined as presence of three of six components, with elevated CRP (≥3 mg/L) or IL-6 (≥2.21 pg/mL) as a sixth component added to NCEP-ATP III criteria. MetS and elevated inflammation markers were independently associated with CHF risk (hazard ratio = 1.32 [95% CI, 1.16–1.51] for MetS; 1.53 [95% CI, 1.34–1.75] for CRP; and 1.37 [95% CI, 1.19–1.55] for IL-6). There was a 20% relative excess risk attributed to the combination of MetS and CRP (95% CI, −44% to 88%). CRP/MetS and IL-6/MetS definitions reclassified 18% and 13%, respectively, of participants as having MetS. Both CRP/MetS and IL-6/MetS increased risk of CHF by 60% compared with those without MetS. In this study, MetS and inflammation markers provided additive information on CHF risk in this elderly cohort.

In a cross-sectional study of 3,873 individuals (weighted to 156 million) aged ≥ 18 years participating in the NHANES 1999–2000, participants were classified as having diabetes, MetS according to modified NCEP-ATP III criteria, or neither condition by low (<1 mg/L), intermediate (1–3 mg/L), or high (>3 mg/L) CRP levels.

Malik et al. [24] reported that after adjusting for age, gender, smoking, and total cholesterol, compared with those with neither MetS nor diabetes and low CRP levels, the odd ratios of CVD were 1.99 (95% CI, 1.10–3.59) for those with no disease and high CRP levels and 2.67 (95% CI, 1.30–5.48) for those with MetS and intermediate CRP. Persons with MetS but high CRP had an OR of 3.33 (95% CI, 1.80–6.16), similar to those with diabetes and low CRP (3.21; 95% CI, 1.27–8.09). The likelihood of CVD was highest in those with diabetes who had intermediate CRP levels (6.01; 95% CI, 2.54–14.20) and in those with diabetes and high CRP (7.73; 95% CI, 3.99–14.95).

Pischon et al. [25] showed in the Nurses' Health Study and Health Professionals Follow-up Study that whereas MetS was a strong predictor of CHD in both men and women, CRP was additive in men only. It should be emphasized that in this study, a modified definition of MetS was used because waist circumference, blood pressure, and glucose were not available at baseline. In a smaller Japanese study by Takeno et al. [26] of 461 patients with acute myocardial infarction, CRP levels were additive to MetS in predicting future major adverse cardiac events. Furthermore, recent investigation relating increased CRP levels and MetS in 1,044 older (≥65 years) individuals has also led to the conclusion that MetS is associated with low-grade systemic inflammation and that the association is mainly supported by a strong independent correlation between waist circumference and high hsCRP levels [27]. Collectively, all these studies support the hypothesis that an increased CRP level in the setting of MetS confers an increased risk of future cardiovascular events.

Additionally, a genome-wide association study has been performed among 6,345 apparently healthy women in whom 336,108 single nucleotide proteins were evaluated as potential determinants of plasma CRP concentration [28]. Overall, seven loci that associate with plasma CRP at levels achieving genome-wide statistical significance were found. Two of these loci (GCKR and 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 was concluded that common variations in several genes involved in metabolic and inflammatory regulation have significant effects on CRP levels, consistent with the identification of CRP as a useful biomarker of risk for incident vascular disease and diabetes.

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 benefits 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 for hsCRP has made its measurement simple and inexpensive. In addition, as hsCRP does not display diurnal variation and demonstrates long-term stability comparable with cholesterol, 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 cardiovascular events in individuals [31]. Overall, it appears that in individuals with MetS, an elevated CRP confers a greater risk for cardiovascular events by activation of monocytes and induction of endothelial cell dysfunction [32].

C-Reactive Protein, Endothelial Dysfunction, and Metabolic Syndrome

Endothelial dysfunction (ED) is now recognized to play a critical role in the initiation and progression of atherosclerotic vascular disease [33–35]. Furthermore, endothelial function assessment by brachial flow-mediated dilatation is a surrogate marker of cardiovascular risk [36, 37] and has been shown to be decreased in MetS [38–43]. It is well established that the individual components of Mets are related to ED. Previous studies have shown that obesity, low HDL cholesterol, impaired glucose tolerance, hypertriglyceridemia, and hypertension are associated with decreased endothelium-dependent vasodilatation [44, 45]. Insulin resistance is also associated with ED [46, 47].

An impressive amount of data now implicates CRP in inducing endothelial cell activation and dysfunction in vitro as well as in vivo [48–52]. Several observations demonstrated that CRP levels correlated inversely with endothelial vasoreactivity in vivo [53, 54].The most compelling data implicating CRP as a determinant of ED were studies demonstrating that human CRP reduced basal and stimulated nitric oxide release from arterial and venous endothelial cells [55, 56]. Our group has explored various mechanistic events involved in CRP-mediated endothelial nitric oxide synthase (eNOS) inhibition and documented that increased NADPH oxidase activation and GTPCH1 downregulation are associated with CRP-mediated eNOS uncoupling in human airway epithelial cells in vitro [57•]. In vivo studies have shown that CRP impairs endothelial vasoreactivity and decreases eNOS activity [48, 49, 51–54]. Guan et al. [58••] showed that a single intravenous injection of adeno-associated virus (AAV)

vector with 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 blood pressure. The authors went on to show impaired endothelium-dependent vasoreactivity in the AAV-hsCRP rats versus the control rats administered AAV-green fluorescent protein. Previously, we have shown that CRP inhibits prostacyclin synthase, resulting in decreased prostacyclin, which is a potent vasodilator [50]. Thus, CRP, by inducing ED, could put individuals with MetS at further risk for hypertension and CVD.

Individuals 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 in endothelial cells [59, 60]. CRP appears to induce PAI-1 antigen and activity via upregulation of nuclear factor-κB (NF-κB) and Rho kinase activities [61].

Individuals with MetS have increased circulating levels of cell adhesion molecules (CAMs). In 943 70-old participants (50% women) of the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, Ingelsson et al. [62] reported that vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and CRP demonstrated the strongest associations with MetS and insulin resistance. Also, in the Women's Health Study, women with MetS had significantly higher CRP and soluble intercellular adhesion molecule-1 (ICAM-1) levels that correlated significantly with increased vascular risk [63]. Furthermore, Kressel et al. [64] showed that individuals with MetS had significantly higher values of CRP, soluble ICAM, and soluble VCAM compared with those without MetS [64]. Rosso et al. [65] demonstrated increased VCAM in individuals with MetS, and this correlated significantly with the quantitative insulin-sensitivity check index (QUICKI). We have previously shown in shear stress and static conditions that CRP upregulates ICAM, VCAM, NF-κB, and monocyte-endothelial cell adhesion in a dose-dependent manner [66].

C-Reactive Protein, Monocyte-Macrophages, and Metabolic Syndrome

The proinflammatory effects of CRP that have been documented in monocyte-macrophages include induction of tissue factor, proinflammatory cytokines, reactive oxygen species, chemokine receptor CCR2, release of matrix metalloproteinase (MMP), CD11b expression, and oxidized LDL uptake as well as inhibition of cholesterol efflux and lipopolysaccharide (LPS)-induced IL-10 release [67–73, 74•]. Another important in vivo demonstration made recently is from our group on the induction of myeloperoxidase activity in macrophages by CRP administration [75].

Several lines of experimental evidence support the role of monocyte chemotactic protein-1 (MCP-1) in atherogenesis, insulin resistance, and adipose tissue-mediated inflammation. Also, CRP has been reported to induce MCP-1 in endothelial cells [76] and its receptor CCR2 on monocytes [69]. Furthermore, Esposito et al. [77] have reported that in both obese and non-obese 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 monocyte-derived macrophages [78].

Recently, Bisoendial et al. [79] examined whole-blood expression for 95 inflammatory markers before and after infusion of 1.25 mg/kg of recombinant human CRP in five male volunteers using quantitative real-time polymerase chain reaction analysis. Relevant transcript levels were measured at baseline and 4 and 8 h after recombinant human CRP infusion. CRP caused significant upregulation of MMP-9, MCP-1, plasminogen activator urokinase, macrophage inflammatory protein 1 α, and NF-κB mRNAs in peripheral leukocytes. mRNA upregulation of MMP-9 and MCP-1 was 17- and 11-fold, respectively. The corresponding increase in plasma protein levels of MMP-9 (78±32 ng/mL to 109±41 ng/mL; P=0.014) and MCP-1 (312±92 pg/mL to 2,590±898 pg/mL; P=0.007) closely mirrored mRNA findings. Thus, MetS individuals, who have persistently high CRP levels, may demonstrate increased leukocyte activation compared with those with low CRP levels, and this may contribute to increased cardiovascular risk in these individuals.

Oxidative stress, mainly superoxide, plays a critical role in the pathogenesis of MetS parameters [80]. Fortuño et al. [80] have reported increased mononuclear cell activation in MetS patients compared with control subjects. They also demonstrate increased superoxide, nitrotyrosine, and oxidized LDL in MetS patients compared with controls, although MetS patients studied in this report were on various medications, including statins (39%) and oral hyperglycemics (21%). Thus, there is an emergent need to study monocyte biology in drug-naïve MetS patients with low and high CRP levels, a subject that has not yet been explored. 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 [55, 57•, 68, 73, 81, 82]. Also, in situ hybridization revealed the presence of CRP mRNA that co-localized with p22phox, an essential component of NADPH oxidase [82]. We also demonstrated in Wistar rats that CRP stimulates superoxide production in macrophages via upregulation of NADPH oxidase [68].

Increased oxidized LDL in the vessel wall and circulation has been shown in patients with acute coronary syndrome and is associated with ED and predicted cardiovascular events [83]. Furthermore, patients with MetS exhibit increased plasma oxidized LDL levels [84]. In addition, we recently showed that CRP promotes oxidized LDL uptake and cholesterol ester accumulation in Wistar rats [74•].

Patients with MetS are in a procoagulant state. Tissue factor is increased in morbidly obese persons with abnormal glucose tolerance compared with those with normal glucose tolerance [85]. Diamant et al. [85] also demonstrated increased tissue factor—containing microparticles in type 2 diabetes mellitus that correlated significantly with features of MetS in this population. In vivo, several lines of evidence indicate that CRP promotes procoagulant activity [41]. We have shown that CRP promotes tissue factor activity in vitro and in vivo in the rat model and shown that it occurs via activation of reactive oxygen species and NF-κB [68].

MMPs and their tissue inhibitors of metalloproteinase (TIMP) may play a role in cardiovascular complications associated with MetS. Studies have shown increased levels of pro-MMP-9, MMP-8, and TIMP-1 in MetS patients compared with controls [86]. Furthermore, we have confirmed in vitro and in vivo that CRP augments MMP-9 release and activity when injected into Wistar rats [74].

NF-κB is a pivotal transcription factor involved in the induction of specific proinflammatory genes [87]. Studies in animal models have demonstrated the importance of IKKβ 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 mononuclear cells, with increased mRNA for TNF [88], IL-6, macrophage inhibitory factor, and MMP-9, consistent with the proinflammatory state. Recently, we have shown that CRP induces NF-κB activity in rat macrophages in vivo [68, 74•]. Also, we have previously shown that in MetS patients, simvastatin therapy decreased hsCRP levels and mononuclear NF-κB activity [89].

Conclusions

Emerging laboratory and clinical evidence has shown a 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 to shed new light on the role of CRP, specifically in mediating vascular effects and conferring increased risk of cardiovascular events in MetS patients with high CRP levels. In this regard, it should be emphasized that the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [90••] study showed a clear benefit of statin therapy in patients with CRP greater than 2 mg/L, and the published evidence base supports a role for statin therapy in MetS [91].

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- •• Of major importance

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