High-Sensitivity C-Reactive Protein Predicts Cardiovascular Risk in Diabetic and Nondiabetic Patients: Effects of Insulin-Sensitizing Treatment with Pioglitazone

Andreas Pfützner, M.D., Ph.D.,¹ Thomas Schöndorf, Ph.D.,¹ Markolf Hanefeld, M.D.,² and Thomas Forst, M.D.¹

Abstract

Systemic inflammatory activity has turned out to play a key pathogenic role in vascular atherosclerosis, insulin resistance, and type 2 diabetes mellitus. Inflammatory biomarkers may therefore be a valuable tool for risk evaluation. Among them, the best evidence to date supports the use of high-sensitivity C-reactive protein (hs-CRP) to monitor insulin resistance and cardiovascular risk in diabetic and nondiabetic individuals. Data suggest that hs-CRP may also participate directly in the process of atherogenesis. A growing number of clinical trials tested the hypothesis that antidiabetic drugs specifically targeting insulin resistance could benefit individuals by reducing inflammation, atherogenesis, and thus cardiovascular risk. One such class are the thiazolidinediones (pioglitazone and rosiglitazone). These agents act as selective ligands of the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPARγ). This article reviewed published data on hs-CRP changes with the thiazolidinedione agent pioglitazone. Here we found pronounced insulin-sensitizing and anti-inflammatory properties in different clinical settings, including diabetic and nondiabetic individuals. Coadministration of pioglitazone to antilipidemic statin therapy resulted in additional effects on low-grade inflammation, and hs-CRP reduction has been demonstrated to occur independently of glucose lowering. The anti-inflammatory effect appeared to be a rapid physiologic reaction on PPARγ activation and could be observed within a short-term interval after starting pioglitazone therapy. In summary, clinical study results underline the benefit of an early insulin resistance treatment to oppose systemic vascular inflammation and cardiometabolic syndrome in patients with elevated levels of high-sensitivity C-reactive protein.


Introduction

Over the last decades, evidence has accumulated that systemic inflammatory activity plays a key pathogenic role in atherosclerosis and cardiovascular disease (CVD). This rationale has led to a search for clinically useful inflammatory biomarkers to improve CVD risk prediction. Prominent among possible candidates is C-reactive

Author Affiliations: ¹IKFE, Institute for Clinical Research and Development, Mainz, Germany; and ²GWT, Dresden, Germany

Abbreviations: (BMI) body mass index, (CVD) cardiovascular disease, (HbA1c) hemoglobin A1c, (HOMA) homeostasis model assessment, (hs-CRP) high-sensitivity C-reactive protein, (LDL) low-density lipoprotein, (PPAR) peroxisome proliferator-activated receptor-γ

Keywords: atherosclerosis, diabetes, hs-CRP, inflammation, insulin resistance, pioglitazone

Corresponding Author: Andreas Pfützner, M.D., Ph.D., IKFE-Institute for Clinical Research and Development, Parcusstr. 8, D-55116 Mainz, Germany; email address AndreasP@ikfe.de
C-reactive protein (CRP) as measured by a highly sensitive assay. C-reactive protein represents the classical acute-phase protein produced in the liver in response to inflammatory stimuli, and plasma levels of high-sensitive C-reactive protein (hs-CRP) provide a sensitive marker of increased inflammatory activity in the arterial wall.

Chronic, systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome, and type 2 diabetes mellitus. Some related metabolic disorders include abdominal adiposity, hypertension, endothelial dysfunction, and glucose intolerance, which often occur in a cluster. Insulin resistance correlates closely with the risk of CVD, explaining some of the excess mortality in type 2 diabetes patients. There appears to be a more-or-less linear relationship of cardiovascular risk to insulin resistance across the spectrum of normoglycemic patients with insulin resistance up to patients presenting with overt type 2 diabetes.

Among inflammatory biomarkers, the best evidence to date supports the use of hs-CRP as an independent predictor of increased CVD risk in diabetic and nondiabetic patients. In addition, numerous clinical trials have established elevated CRP levels to be predictive of the development of insulin resistance, metabolic syndrome, and type 2 diabetes. Chronic systemic low-grade inflammation may induce insulin resistance, and this association has prompted studies to evaluate the hs-CRP-reducing effects of antidiabetic drugs that work by targeting insulin resistance directly. One such class are the thiazolidinediones (pioglitazone and rosiglitazone). These agents act as selective ligands of the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPARγ). Our institute for clinical research and development performed and conducted multiple studies in various clinical settings and patient populations, which evaluated the role of pioglitazone treatment for the management of insulin resistance, type 2 diabetes, and chronic systemic inflammation. The purpose of this review was to provide an overview about published data that specifically illuminate the impact of pioglitazone on hs-CRP concentrations in diabetic and nondiabetic patients.

Role of hs-CRP in Atherogenesis

Recent scientific research has revealed that increased focal inflammatory activity in the arterial wall is one of the main characteristics of atherosclerosis. From a pathological point of view, all stages of the atherosclerotic process, from its initiation to plaque rupture, might be considered an inflammatory response to injury and endothelial dysfunction. Damage to the endothelial wall triggers a cascade of events that modulates the inflammatory response, leading to the recruitment of white blood cells into the blood vessel wall, where they give rise to abnormal foam cells and initiate the development of atherosclerotic lesions.

Among emerging biomarkers that reflect this inflammatory process, one of the largest databases exists for hs-CRP: a chronic low-level increase of the acute-phase protein turned out to be predictive of the risk of future cardiovascular events. Data suggest that C-reactive protein, beyond its role as a cardiovascular risk marker, may also participate directly in atherogenesis which includes but is not limited to the following effects (Figure 1).

- C-reactive protein binds the phosphocholine of oxidized low-density lipoprotein (LDL).
- C-reactive protein increases LDL uptake into macrophages and enhances the ability of macrophages to form foam cells.
- C-reactive protein inhibits endothelial nitric oxide synthase expression in endothelial cells. Nitric oxide has important antiatherogenic effects, including decreased platelet aggregation, vasoconstriction, and smooth muscle cell proliferation.
- C-reactive protein increases plasminogen activator inhibitor-1 expression and activity.
- C-reactive protein activates macrophages to secrete tissue factor, a powerful procoagulant.
- C-reactive protein upregulates the expression of adhesion molecules in endothelial cells that will attract monocytes to the site of injury.

High concentrations of CRP mRNA have been demonstrated to be present in atherosclerotic plaques. Two research groups revealed independently that CRP is produced by human artery smooth muscle cells of atherosclerotic lesions in response to inflammatory cytokines. Taking all this evidence into account, locally produced CRP may actually participate directly in aspects of atherogenesis, promoting the development of cardiovascular complications.
Role of hs-CRP in Cardiovascular Risk Prediction

A number of large, prospective epidemiologic studies have examined inflammatory markers as predictors of CVD events in different clinical settings. At present, the best characterized biomarker is hs-CRP. Low-level increases in C-reactive protein appear to be a strong independent predictor of future cardiovascular events, including myocardial infarction, ischemic stroke, peripheral vascular disease, and sudden cardiac death among individuals with and without prior evidence of cardiovascular disease (Figure 2).16,31–36

Extensive analysis has demonstrated that hs-CRP adds prognostic information to traditional risk assessment and predicts cardiovascular risk independently of traditional risk factors, including low-density lipoprotein cholesterol.33,37,38 Measurement of hs-CRP in 27,632 initially healthy U.S. women from the Women’s Health Study revealed a predictive value to all LDL cholesterol cutoff points.2 A further analysis in 15,632 participants of a prospective cohort study yielded, after adjustment for age, blood pressure, smoking, diabetes, and obesity, that hs-CRP added prognostic information beyond that conveyed by all lipid measures.39
High-Sensitivity C-Reactive Protein Correlates with Insulin Resistance and Metabolic Syndrome

C-reactive protein has been shown to impair insulin signaling, and emerging laboratory and epidemiological data now link inflammation and hs-CRP to insulin resistance and the metabolic syndrome. We conducted a cross-sectional study to assess the association of hs-CRP levels with insulin resistance, β-cell dysfunction, and the prevalence of macrovascular dysfunction in 4270 noninsulin-treated patients with type 2 diabetes mellitus. Results demonstrated that increased hs-CRP levels were linked to homeostatic model assessment, intact proinsulin, insulin, body mass index (BMI), and β-cell dysfunction (all \( p < 0.001 \))(Figure 3), but showed no correlation with disease duration or glucose control.

Another cross-sectional trial of participants in the Women's Health Study correlated hs-CRP with insulin resistance in nondiabetic women. The odds ratio for having elevated fasting insulin increased with each tertile of hs-CRP. The Insulin Resistance Atherosclerosis Study explored relationships among cardiovascular risk factors, cardiovascular disease, and insulin resistance as measured directly by a frequently sampled intravenous glucose tolerance test across different ethnic groups and various states of glucose tolerance. Results confirmed that CRP was related independently to insulin sensitivity in healthy, nondiabetic subjects and that chronic subclinical inflammation emerged as part of insulin resistance and other components of the metabolic syndrome.

Some authors hypothesized that decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiological effect of insulin on hepatic acute-phase protein synthesis. Clamp studies in normal subjects showed that insulin exerts selective effects on hepatic protein synthesis, reducing the expression of acute-phase response proteins. Resistance to this effect would then in turn lead to increased synthesis of acute-phase proteins, such as CRP. In addition, insulin resistance leads to compensating increased insulin secretion by β cells, supporting visceral lipid tissue growth when sufficient caloric uptake occurs. This process results in an enhanced production of proinflammatory cytokines from the adipose tissue. These proinflammatory cytokines may also contribute to higher levels of C-reactive protein and further impair insulin sensitivity.

Insulin resistance is generally accepted as one of the key components of the metabolic syndrome, a cluster of conditions known to increase the risk of developing type 2 diabetes and CVD. General features of the metabolic syndrome include abdominal obesity, hypertriglyceridemia, high-density lipoprotein (HDL) cholesterol, hypertension, and abnormal glucose. All these attributes, however, have been proven to be associated with chronic, low-grade inflammation, as defined by hs-CRP measurement.

High hs-CRP levels were also found to be strongly correlated and independently with type 2 diabetes: Elevated levels of hs-CRP remained a significant predictor for future diagnosis of metabolic syndrome and diabetes even after adjusting for BMI, family history of diabetes mellitus, smoking, and other factors.

Effects of Pioglitazone Treatment on hs-CRP Reduction

The recognition that chronic low-grade inflammation plays a fundamental role in atherosclerosis, insulin resistance, and type 2 diabetes has led to clinical studies evaluating whether the treatment of insulin resistance (e.g., with thiazolidinediones) may also reduce hs-CRP as biomarker and conceivable risk factor of cardiovascular disease. Thiazolidinediones (pioglitazone and rosiglitazone) are a class of insulin-sensitizing agents used to treat type 2 diabetes mellitus. For pioglitazone therapy, the PROactive study revealed significant reductions in secondary cardiovascular outcome measures, including macrovascular death, reinfarction, and restroke. Because chronic inflammation may be an underlying...
cause of both atherosclerosis and insulin resistance, treatments with anti-inflammatory properties may also reduce the incidence of macrovascular complications associated with insulin-resistant states. Indeed, studies have demonstrated that pioglitazone therapy benefits individuals with elevated hs-CRP values.\textsuperscript{46–53} Table 1 provides an overview of the growing number of clinical trials that have examined the impact of pioglitazone on inflammatory processes as measured by hs-CRP levels in various clinical settings.

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$^a$ Abbreviations: ATOR, atorvastatin; GLIM, glimepiride; HDL-C, high-density lipoprotein cholesterol; MET, metformin; MetSyn, metabolic syndrome; mono, monotherapy; PBO, placebo; PIO, pioglitazone; RAM, ramipril; SIM, simvastatin; SU, sulfonylureas.

$^b$ Greater than 1% of reduction in HbA1c.
In 2003, Satoh et al. published data of 136 Japanese type 2 diabetes patients showing that pioglitazone treatment (30 mg daily for 3 months) significantly reduced hyperglycemia and hs-CRP relative to an untreated control group. In fact, a stratification into glycemic control responders [≥1% of reduction in hemoglobin A1c (HbA1c)] and nonresponders revealed that CRP reduction with pioglitazone occurred independently of changes in parameters related to glucose metabolism. Similar results are now emerging from numerous clinical trials, reinforcing the anti-inflammatory potential of this thiazolidinedione.

The Pioneer study enrolled 192 type 2 diabetes patients into a 6-month, prospective, open-label trial. The patients were randomized to receive either pioglitazone (45 mg) or glimepiride (1 to 6 mg, with the intent to optimize therapy). Significant reductions in hs-CRP were only observed in the pioglitazone group (p < 0.05 vs glimepiride). Both groups achieved a comparable reduction in HbA1c (p < 0.001), suggesting an independent effect of pioglitazone to improve hs-CRP as a measure of low-grade inflammation. The multicenter, double-blinded, and placebo-controlled PIOcard study investigated inflammatory markers during pioglitazone treatment in 92 type 2 diabetes patients with angiographically proven coronary heart disease. An 18% reduction in hs-CRP levels (p < 0.05 vs placebo) was observed after only 3 days of treatment with pioglitazone. We concluded that even before effects on glucose metabolism could be obtained, pioglitazone exerted immediate effects on plasma markers of inflammation. The PioSwitch study converted 98 type 2 diabetes patients with residual β-cell function from insulin therapy to treatment with pioglitazone and glimepiride for 6 months. For the majority of patients, the switch from insulin therapy was possible without deterioration of blood glucose control and resulted in a significant decrease of hs-CRP levels (p < 0.01 vs baseline). A combined pioglitazone and metformin treatment study with 14 type 2 diabetes patients examined the efficacy of short-term intravenous insulin intervention followed by oral pioglitazone and metformin therapy to prevent patients from continuous insulin applications. Initially, an in-patient, 34-hour continuous intravenous insulin infusion was performed and metformin was given (2 × 850 mg/day). Insulin was stopped and 30 mg/day pioglitazone was added at the second in-patient day. Participants were followed for another 4 months. Results demonstrated that a beneficial effect of a short-term intravenous insulin application on glycemic control could be maintained effectively by pioglitazone/metformin treatment. Improvements in hs-CRP values were demonstrated at end point only after continued glitazone intake (p < 0.05 vs baseline). Analyses of data from the IRIS V study, a large population-based observational trial in a routine clinical setting, substantiated the favorable effects of the insulin-sensitizing agent on systemic chronic inflammation: 1170 subjects received pioglitazone alone or in combination with their previous treatment (acarbose, sulfonylurea drugs, and/or metformin). After 20 weeks, hs-CRP levels had decreased significantly with pioglitazone therapy (baseline 3.3 ± 1.0 mg/liter vs end point 2.8 ± 2.3 mg/liter, p < 0.01). The PIOglim study was a double-blind, parallel prospective study with 82 patients with type 2 diabetes mellitus treated previously with sulfonylurea monotherapy with insufficient glycemic control (HbA1c >7.0%). They were randomized either to up titration of glimepiride (4 to 6 mg; n = 37; 22 males, 15 females, age: 60 ± 9 years, HbA1c: 7.5 ± 0.6%, BMI: 31.6 ± 5.7 kg/m²) or to receive a glimeperide + pioglitazone combination (up titration possible with 2 mg + 30 mg, 4 mg + 30 mg, and 4 mg + 45 mg; 30/45 mg, n = 45; 25 males, 20 females, age: 62 ± 8 years, HbA1c: 7.2 ± 0.6%, BMI: 33.5 ± 6.2 kg/m²) for the next 6 months. A reduction in HbA1c was observed in both groups, which was less pronounced in the glimeperide up titration group (absolute percent: −0.30%, p < 0.05 vs baseline) than in the combination group (−0.84%, p < 0.001). The combination group also showed a pronounced relative reduction in hs-CRP from −32.6%, which was more extensive than in the comparator group (−8.1%). The effect of a fixed combination of pioglitazone (15 mg) with metformin (850 mg) given twice daily in comparison to a glimepiride + metformin combination therapy on diabetic dyslipidemia and chronic systemic inflammation was assessed in the double-blind, randomized parallel PIOfix study with 288 patients (187 males, 101 females, age: 59 ± 10 years, BMI: 32.6 ± 5.1 kg/m², HbA1c: 7.3 ± 0.8%). Although similar improvements in HbA1c were seen with both treatments within 6 months, the pioglitazone + metformin combination had a significantly better effect on triglycerides and HDL cholesterol, and a pronounced hs-CRP improvement was seen in this arm (−0.9 ± 1.9 mg/dl), whereas no effect on hs-CRP could be observed with the glimepiride + metformin combination (0.0 ± 1.8 mg/liter, p < 0.001).

Insulin resistance may also be present in normoglycemic individuals, and some of these patients can be diagnosed as having (cardio)metabolic syndrome. Research in these study populations confirmed the efficacy of pioglitazone treatment for reducing chronic systemic inflammation and hs-CRP levels independently from glucose-lowering.

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mechanisms. Our own investigations examined insulin-sensitizing effects on CRP levels compared to the impact of lipid-lowering and antihypertensive therapy in patients at increased macrovascular risk.\(^{47,49,53}\)

The PIOSTAT study demonstrated that nondiabetic patients with vascular insulin resistance and dyslipidemia treated with pioglitazone therapy experienced an overall reduction in chronic systemic inflammation, which was significantly more pronounced than with alternative simvastatin therapy. Giving both drugs in combination resulted in a synergistic effect on the inflammatory biomarker hs-CRP.\(^{47}\) Insulin resistance as measured by homeostasis model assessment (HOMA) decreased in those receiving pioglitazone, and the correlation between changes in HOMA and hs-CRP was significant \((r = 0.43; p < 0.05)\). The PIOVASC study investigated the anti-inflammatory effects of atorvastatin monotherapy and combined treatment with atorvastatin and pioglitazone in 148 patients (BMI 29.2 ± 4.1 kg/m\(^2\)) with increased cardiovascular risk. Again, the addition of pioglitazone to atorvastatin resulted in a significant further reduction of high-sensitivity C-reactive protein \((p < 0.05)\).\(^{49}\) The primary objective of the PIOace study was to investigate the effects of pioglitazone, ramipril, or their combination on low-grade inflammation in nondiabetic hypertensive individuals. Patients were treated with 30/45 mg pioglitazone (dose titration), 2.5/5 mg ramipril, or their combination for 12 weeks. A reduction in hs-CRP was observed with pioglitazone \((-0.89 ± 1.98 \text{ mg/liter})\) and combination therapy \((-0.49 ± 2.11 \text{ mg/liter})\), whereas an increase occurred with ramipril therapy alone \((0.58 ± 2.13 \text{ mg/liter})\). Improvements in insulin sensitivity were seen in the pioglitazone and the combination arms only, supporting the link between insulin resistance and chronic low-grade inflammation.\(^{53}\)

A summary of hs-CRP changes observed in our interventional controlled trial, adjusted for the activity of comparator treatments, is provided in Figure 4. Combined analysis revealed an overall reduction of hs-CRP by 26.8% in diabetic patients, by 28.4% in nondiabetic patients with metabolic syndrome, and an overall reduction by 27%.

Available study data suggest that rosiglitazone, the other currently available thiazolidinedione, may have similar effects on hs-CRP reduction in diabetic and nondiabetic patients.\(^{57-64}\) Analyses from a study entitled A Diabetes Outcome Progression Trial examined long-term effects of rosiglitazone, glyburide, and metformin on hs-CRP in 904 diabetic subjects over 4 years: CRP decreased more markedly in the rosiglitazone group by \(-47.6\% \text{ relative to glyburide and } -30.5\% \text{ to metformin at 48 months}\).\(^{64}\)

Evidence for anti-inflammatory activity of insulin itself remains controversial. Data appeared that newly initiated insulin therapy in patients with poorly controlled type 2 diabetes decreased serum hs-CRP.\(^{68}\) Another trial pointed out that the decrease in CRP was significantly more pronounced in intensive insulin-treated patients compared to conventional insulin therapy.\(^{69}\) In contrast to this, improvement in glycemic control with insulin monotherapy was not associated with a
parallel improvement in markers of vascular inflammation in young, obese, type 2 diabetes patients.\textsuperscript{70}

**Lifestyle Modification**

A higher body mass index was proved to be linked to insulin resistance and elevated CRP concentrations, suggesting a state of low-grade systemic inflammation in overweight and obese persons.\textsuperscript{9} Nondrug strategies used to reduce insulin resistance include diet and physical activity. Accordingly, effective weight loss has been shown to reverse elevated hs-CRP levels in diabetic and nondiabetic populations.\textsuperscript{9,11,71,72} Favorable effects on the inflammatory response, including a decrease in hs-CRP levels, have also been seen with physical activity interventions.\textsuperscript{72,73}

**High-Sensitivity C-Reactive Protein in Daily Clinical Practice**

It is important to distinguish between standard and high sensitivity assays for the measurement of CRP. The traditional CRP assay, using a polyclonal antibody, assists in the diagnosis and assessment of acute inflammation, i.e., associated with infections and neoplastic diseases. A more sensitive CRP test, the highly sensitive C-reactive protein assay, allows detection of CRP levels down to and below 3 mg/liter. These lower levels toward the upper end of normal reflect low-grade inflammation and have a predictive value of future risk for CVD events.\textsuperscript{72}

Measurement of hs-CRP should be done twice, optimally 2 weeks apart, to provide a more stable estimate of level of this marker. The relative cardiovascular risk categories for average hs-CRP levels are:\textsuperscript{24}

- low risk <1.0 mg/liter
- average risk 1.0–3.0 mg/liter
- high risk 3.0–10.0 mg/liter
- unspecific elevation >10 mg/liter (should be reevaluated for acute inflammatory conditions)

**Conclusions and Summary**

The excess cardiovascular risk in insulin-resistant patients is substantial. Research of recent decades revealed that low-grade inflammation is linked significantly to insulin resistance, type 2 diabetes, and increased risk of cardiovascular disease. Elevated levels of high-sensitivity C-reactive protein emerged as a reliable biomarker for the subclinical inflammatory state. Current evidence supports the usefulness of hs-CRP measurement for vascular risk and treatment efficacy assessment in insulin-resistant diabetic and nondiabetic individuals.

Therapies that address insulin resistance may benefit individuals by reducing inflammation, atherogenesis, and thus macrovascular complications. Treatment aimed at improving the insulin-resistant state, whether nonpharmacological, such as exercise and weight reduction, or pharmacological, such as metformin and thiazolidinediones, results in a decrease of CRP levels beyond mere glucose lowering.

For the thiazolidinedione drug pioglitazone, we proved both pronounced insulin-sensitizing and anti-inflammatory properties in different clinical settings. Coadministration of pioglitazone to antilipidemic statin therapy resulted in additional effects on low-grade inflammation, and hs-CRP reduction has been demonstrated to occur independently from glucose lowering. The anti-inflammatory effect appears to be a rapid physiologic reaction on PPAR\(\gamma\) activation and can be observed within a short-term interval after starting a pioglitazone therapy. In summary, results underline the benefit of an early insulin resistance treatment to oppose systemic vascular inflammation and the cardiometabolic syndrome in diabetic and nondiabetic individuals with elevated levels of high-sensitivity C-reactive protein.
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