Effect of Atorvastatin and Irbesartan, Alone and in Combination, on Postprandial Endothelial Dysfunction, Oxidative Stress, and Inflammation in Type 2 Diabetic Patients

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Background—Postprandial hypertriglyceridemia and hyperglycemia are considered risk factors for cardiovascular disease. Evidence suggests that postprandial hypertriglyceridemia and hyperglycemia induce endothelial dysfunction and inflammation through oxidative stress. Statins and angiotensin type 1 receptor blockers have been shown to reduce oxidative stress and inflammation, improving endothelial function.

Methods and Results—Twenty type 2 diabetic patients ate 3 different test meals: a high-fat meal, 75 g glucose alone, and a high-fat meal plus glucose. Glycemia, triglyceridemia, endothelial function, nitrotyrosine, C-reactive protein, intercellular adhesion molecule-1, and interleukin-6 were assayed during the tests. Subsequently, diabetics took atorvastatin 40 mg/d, irbesartan 300 mg/d, both, or placebo for 1 week. The 3 tests were performed again between 5 and 7 days after the start of each treatment. High-fat load and glucose alone produced a decrease in endothelial function and increases in nitrotyrosine, C-reactive protein, intercellular adhesion molecule-1, and interleukin-6. These effects were more pronounced when high-fat load and glucose were combined. Short-term atorvastatin and irbesartan treatments significantly counterbalanced these phenomena, and their combination was more effective than either therapy alone.

Conclusions—This study confirms an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial function and inflammation, suggesting oxidative stress as a common mediator of such an effect. Short-term treatment with atorvastatin and irbesartan may counterbalance this phenomenon; the combination of the 2 compounds is most effective. (Circulation. 2005;111:2518-2524.)

Key Words: endothelium • hyperglycemia • inflammation • oxidative stress

Patients with diabetes have an increased risk of cardiovascular disease (CVD). Recently, much attention has been paid to evidence that abnormalities of the postprandial state are important contributing factors to the development of atherosclerosis, even in diabetes mellitus. In nondiabetic subjects, there is evidence that postprandial hypertriglyceridemia is a risk factor for CVD, whereas in diabetic subjects, postprandial hyperglycemia has recently been proposed as an independent risk factor for CVD. Because in diabetic patients the postprandial phase is characterized by a simultaneous increase in both plasma triglycerides and glucose, the distinct role and relative importance of these 2 factors in the pathogenesis of CVD in diabetes are a matter of debate.

The response-to-injury hypothesis of atherosclerosis states that the initial damage affects the arterial endothelium, leading to endothelial dysfunction. Moreover, the concept of atherosclerosis as an inflammatory disease, even in diabetes, is now well established. Indeed, endothelial dysfunction has been demonstrated in patients with diabetes, and hyperglycemia has been implicated as a cause of endothelial dysfunction in normal and diabetic subjects. Similarly, a negative influence of postprandial hypertriglyceridemia on endothelial function has been reported in both normal and diabetic subjects. Furthermore, studies support the evidence that acute hyperglycemia during a hyperglycemic clamp or in the postprandial state can induce inflammation as postprandial hypertriglyceridemia.

It has been suggested that hyperglycemia and hypertriglyceridemia induce endothelial dysfunction and inflammation through the production of an oxidative stress. Indeed, recent studies demonstrate both an independent and a cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial function, with oxidative stress the common mediator. The production of oxidative stress in such conditions may involve the overgeneration of superoxide anion (O₂⁻) at the mitochondrial level, which in turn...
TABLE 1. Baseline Characteristics of the Control and Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=20)</th>
<th>Diabetics (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>12/8</td>
<td>12/8</td>
</tr>
<tr>
<td>Age, y</td>
<td>53.5±2.5</td>
<td>52.2±2.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4±2.1</td>
<td>29.8±2.5</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.8±0.2</td>
<td>7.3±1.4*</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.8±0.2</td>
<td>7.5±0.3*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118.3±7.5</td>
<td>121.7±4.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78.4±2.1</td>
<td>82.8±4.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.5±0.6</td>
<td>5.2±1.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9±0.2</td>
<td>2.7±1.4*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>1.4±0.2</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>2.5±0.3</td>
<td>2.6±0.4</td>
</tr>
<tr>
<td>FMD, %</td>
<td>12.3±0.9</td>
<td>5.9±0.8*</td>
</tr>
<tr>
<td>NT, µmol/L</td>
<td>0.23±0.5</td>
<td>0.66±0.3*</td>
</tr>
<tr>
<td>ICAM-1, mg/mL</td>
<td>144.6±22.7</td>
<td>265.5±15.4*</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.2±0.4</td>
<td>3.1±0.9*</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>0.9±0.2</td>
<td>2.8±0.9*</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL-C, HDL cholesterol; and LDL-C, LDL cholesterol. Data are expressed as mean±SEM. *P<0.001 vs control subjects.

None of the subjects was taking aspirin, lipid-lowering agents, blood pressure-lowering drugs, or supplemental vitamins. Diabetes was treated with diet alone in all the patients; the duration of disease was 5.4±2.1 years (mean±SEM). All subjects were recommended to consume their habitual diets during the entire study period.

Written consent was obtained from all subjects. The local ethics committee approved the study.

Study Design
At the end of a 4-week placebo run-in period, blood samples were taken, and fasting glycemia, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, NT, C-reactive protein, intercellular adhesion molecule (ICAM)-1, interleukin (IL)-6, and HbA1c were measured. Blood pressure and endothelial function also were measured. Diabetic patients ate, in randomized order, 3 different menus on 3 different days: test 1, a high-fat meal; test 2, 75 g glucose alone; and test 3, a high-fat meal plus 75 g glucose. Blood samples were drawn at 0, 1, 2, 3, and 4 hours, and the following variables were assayed: glycemia, triglyceridemia, NT, C-reactive protein, ICAM-1, IL-6, and endothelial function. Studies were begun at 8 AM after a 12- to 14-hour overnight fast.

Subsequently, a double-blind, crossover, placebo-controlled study was started. All diabetic patients were randomly assigned to take placebo or atorvastatin 40 mg/d, irbesartan 300 mg/d, or atorvastatin 40 mg/d plus irbesartan 300 mg/d for 7 days. The washout period between each treatment period was 2 weeks. At baseline and after 4 days of treatment, the following parameters were measured: fasting glycemia, serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HbA1c, NT, C-reactive protein, ICAM-1, IL-6, blood pressure, and endothelial function. The 3 above-described meal tests were then performed between 5 and 7 days after the start of each treatment.

High-Fat Load
The standardized high-fat meal consisted of whipping cream and contained 75 g fat, 5 g carbohydrates, 6 g proteins per 1 m² body surface area. The corresponding caloric intake was 700 kcal/m².

Biochemical Measurements
Cholesterol and triglycerides were measured enzymatically (Roche Diagnostics). HDL cholesterol was estimated after precipitation of apolipoprotein B with phosphotungstate/magnesium. LDL cholesterol was calculated after lipoprotein separation. Plasma glucose was measured by the glucose-oxidase method, and HbA1c was assessed by high-performance liquid chromatography. NT was measured by ELISA as previously described. C-reactive protein, ICAM-1, and IL-6 plasma concentration were assayed by commercially available ELISA kits (Bender MedSystems Diagnostics GmbH).

Endothelial Function
Endothelial function was evaluated by measuring the flow-mediated vasodilation (FMD) of the brachial artery. Vasodilation responses of the brachial arteries were measured by ultrasound technique by 2 skilled examiners. The validity of this method has been confirmed in previous studies. Briefly, the diameter of the brachial artery was measured from B-mode ultrasound images with a 7.5-MHz linear-array transducer (SSH-160A, Toshiba). Flow velocity in the brachial artery was measured with a pulsed Doppler signal at a 70° angle to vessel, with the range gate (1.5 mm) in the center of the artery. The brachial artery was scanned in the antecubital fossa in a longitudinal fashion. Depth and gain settings, optimized at the beginning of the study, were kept constant throughout the recording period. When a satisfactory transducer position was found, the surface of the skin was marked, and the arm remained in the same position throughout the study. Each subject lay quietly for 10 minutes before the first scan.

At the end of each test, the subjects lay quietly for 15 minutes. Then, sublingual nitroglycerin (0.3 mg) was administered; 3 minutes later, the last measurements were performed. Response to nitroglycerine.
erin was used as a measure of endothelium-independent vasodilation. All studies were performed in a quiet and temperature-controlled room (22°C to 23°C).

After baseline measurements of the diameter of and flow velocity in the brachial artery, a blood pressure cuff placed around the forearm was inflated with a pressure of 250 to 300 mm Hg and released after 5 minutes. Measurements of diameter and flow velocity were continuously performed from cuff inflation to due time after cuff deflation. The ultrasound images were recorded on a super VHS videocassette recorder (BR-S601 mol/L, Victor), and arterial diameter was measured at a fixed distance from an anatomical marker with ultrasonic calipers by 2 independent observers. Measurements were taken from the anterior to the posterior interface between the media and adventitia (“m” line) at the end of diastole, coincident with the R wave on a continuously recorded ECG.24 The diameters of 4 cardiac cycles were analyzed for each scan, and the measurements were averaged. Diameter measurements for the reactive hyperemia and nitroglycerin were expressed as the percent increase calculated by multiplying the velocity-time integral of the Doppler flow signal by heart rate and vessel cross-sectional area. The increase in glycemia during the oral glucose tolerance test was accompanied by a significant decrease in FMD at 1, 2, and 3 hours in diabetic patients (P<0.05 versus baseline; Figure 1). The increase in glycemia during the oral glucose tolerance test was accompanied by a significant decrease in FMD at 1, 2, and 3 hours in diabetic patients (P<0.05 versus baseline; Figure 1).

Figure 1. Effects of high-fat load, oral glucose tolerance test (OGTT), and their combination in diabetic patients. Bars indicate SEM.

Results

Baseline glycemia, HbA1c, triglycerides, NT, C-reactive protein, ICAM-1, and IL-6 were increased in diabetic patients, whereas FMD was reduced (Table 1).

Compared with preprandial values, serum triglycerides were increased from 1 to 4 hours (P<0.05 versus baseline; Figure 1) during the high-fat meal and the high-fat meal plus 75 g glucose. Glycemia increased at 1, 2, and 3 hours in diabetics during the 75-g glucose challenge and the high-fat meal plus 75 g glucose (P<0.05 versus baseline; Figure 1), whereas triglycerides remained unchanged during the 75-g glucose challenge alone (Figure 1).

High-fat load alone produced a decrease in FMD and increases in NT, C-reactive protein, ICAM-1, and IL-6 from 1 to 4 hours (P<0.05 versus baseline; Figure 1). The increase in glycemia during the oral glucose tolerance test was accompanied by a significant decrease in FMD at 1, 2, and 3 hours in diabetic patients (P<0.05 versus baseline; Figure 1), returning to basal values only at 4 hours (Figure 1). NT, C-reactive protein, ICAM-1, and IL-6 concentration changed during the studies; those variations were opposite those of FMD (P<0.05 versus baseline; Figure 1).

The combination of high-fat and glucose load, ie, test 3, produced a decrease in FMD and increases in NT, C-reactive protein, ICAM-1, and IL-6 (P<0.05 versus baseline; Figure 1), even more pronounced than with either nutrient alone (P<0.05; Figure 1).

Short-term atorvastatin treatment, alone or in combination with irbesartan, had no effect on lipid parameters in diabetic patients (Table 2). However, significant improvements in basal FMD, NT, C-reactive protein, ICAM-1, and IL-6 were observed (Table 2). The values after 4 days of treatment were considered for the comparison to avoid a possible interference of the tests performed in the last 3 days of the treatment. Such treatment was able to reduce the effect on endothelial function, NT, C-reactive protein, ICAM-1, and IL-6 observed during every test, even though postprandial hypertriglyceridemia was not affected (P<0.05 versus placebo; Figures 2 through 4).

Short-term irbesartan treatment, alone or in combination, had no effect on lipid parameters or blood pressure in diabetic patients (Table 2). However, as with atorvastatin treatment, short-term irbesartan treatment, alone or in combination, had no effect on lipid parameters or blood pressure in diabetic patients (Table 2).
function and NT, C-reactive protein, ICAM-1 and IL-6 observed during every test (P<.05 versus placebo; Figures 2 through 4).

Short-term combination therapy produced a more marked improvement in all the studied parameters both in basal conditions and during each test compared with the single treatments (Figures 2 through 4).

Endothelium-independent vasodilation was not affected during the studies (data not shown).

Discussion

This study confirms that in diabetic patients both postprandial hyperglycemia and hypertriglyceridemia have an independent and cumulative effect in favoring endothelial dysfunction accompanied by generation of oxidative stress and inflammation. The data also confirm that statins, atorvastatin in this case, can counterbalance this effect. The action of atorvastatin is reasonably due to its ancillary properties, being evident after short-term administration, which does not influence the lipid profile, either fasting or postprandial. A protective effect of AT-1 receptors blockers on endothelial function during postprandial hypertriglyceridemia has been reported in healthy subjects. Our results show, for the first time, that the AT-1 receptor blocker irbesartan, like statins, is also effective in counterbalancing the effect of both postprandial hyperglycemia and hypertriglyceridemia on endothelial function, oxidative stress, and inflammation in diabetic patients. Even for irbesartan, the results are not linked to the blood pressure–lowering effect and are obtained after a short-term treatment. In our opinion, however, the most interesting finding is that the combination of atorvastatin and irbesartan shows a more powerful effect.

Statin and AT-1 receptor blockers protect endothelial function and reduce inflammation in diabetic and non-diabetic subjects, and these effects are convincingly mediated through their intracellular antioxidant activity. Interestingly, the ability of irbesartan to reduce the proteinuria independently from its blood pressure–lowering action has also been confirmed in a study with an ad hoc design, suggesting that AT-1 receptor blockers may have a protective effect on diabetes-related complications through some ancillary properties.

It has been suggested that both hyperglycemia and hyperlipidemia may damage the vascular system, particularly endothelial cells, producing oxidative stress. The proposed mechanism leading to oxidative stress during both hyperglycemia and hypertriglyceridemia is that acetylCoA, from either glucose derived through pyruvate or β-oxidation of free fatty acids derived from triglycerides, overloads mitochondria in such conditions. The mitochondrial proton gradient increases, and single electrons are transferred to oxygen, leading to the formation of free radicals, particularly superoxide anion.

Today, this particular process is considered of great relevance in diabetes. Recent studies demonstrate that a single hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain seems to be the first and key event in the activation of all other pathways involved in the development of endothelial dysfunction and in the pathogenesis of diabetic complications. Superoxide overproduction is accompanied by increased NO generation resulting from endothelial NO synthase and inducible NO synthase uncoupled state, a phenomenon favoring the formation of the strong oxidant peroxynitrite, which in turn damages DNA. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose) polymerase. Poly(ADP-ribose) polymerase activation in turn depletes the intracellular concentration of its substrate NAD+, slowing the rate of glycolysis, electron transport, and ATP formation, and produces an ADP-ribosylation of GAPDH. These processes result in the activation of all pathways involved in development of dia-

### Table 2. Effects of Short-Term Placebo, Atorvastatin, Irbesartan, and Atorvastatin Plus Irbesartan Treatments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Days of Placebo</th>
<th>4 Days of Atorvastatin</th>
<th>4 Days of Irbesartan</th>
<th>4 Days of Atorvastatin + Irbesartan</th>
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</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>29.8±2.5</td>
<td>29.8±2.3</td>
<td>29.7±2.4</td>
<td>29.8±2.2</td>
<td>29.8±2.4</td>
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<tr>
<td>Fasting glucose, mmol/L</td>
<td>7.2±1.2</td>
<td>7.1±1.5</td>
<td>7.0±1.3</td>
<td>7.3±1.0</td>
<td>7.0±1.2</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.5±0.3</td>
<td>7.5±0.4</td>
<td>7.5±0.6</td>
<td>7.5±0.3</td>
<td>7.6±0.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123.5±4.6</td>
<td>120.4±6.6</td>
<td>121.9±5.2</td>
<td>125.3±3.6</td>
<td>121.2±3.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82.5±4.7</td>
<td>84.2±5.1</td>
<td>82.4±5.5</td>
<td>84.3±2.9</td>
<td>82.2±6.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.0±1.5</td>
<td>5.0±1.7</td>
<td>5.2±1.3</td>
<td>5.3±1.6</td>
<td>5.2±1.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.6±1.5</td>
<td>2.8±1.6</td>
<td>2.8±1.4</td>
<td>2.7±1.9</td>
<td>2.6±1.2</td>
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<tr>
<td>HDL-C, mmol/L</td>
<td>1.1±0.5</td>
<td>1.2±0.4</td>
<td>1.1±0.6</td>
<td>1.2±0.5</td>
<td>1.2±0.5</td>
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<tr>
<td>LDL-C, mmol/L</td>
<td>2.6±0.7</td>
<td>2.6±0.3</td>
<td>2.3±0.6</td>
<td>2.5±0.5</td>
<td>2.5±0.9</td>
</tr>
<tr>
<td>FMD, %</td>
<td>5.8±0.4</td>
<td>5.7±0.7</td>
<td>7.6±0.6*</td>
<td>7.8±0.6*</td>
<td>9.8±0.3*†</td>
</tr>
<tr>
<td>NT, μmol/L</td>
<td>0.59±0.7</td>
<td>0.62±0.4</td>
<td>0.40±0.2*</td>
<td>0.43±0.4*</td>
<td>0.31±0.5†</td>
</tr>
<tr>
<td>ICAM-1, ng/mL</td>
<td>268.5±16.4</td>
<td>271.5±13.2</td>
<td>228.5±10.4</td>
<td>227.7±10.2*</td>
<td>198.5±10.1†</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>3.0±0.8</td>
<td>3.1±0.7</td>
<td>2.3±0.8*</td>
<td>2.3±0.5*</td>
<td>1.7±0.4†</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.8±0.7</td>
<td>2.9±0.5</td>
<td>2.0±0.2*</td>
<td>2.0±0.3*</td>
<td>1.5±0.5†</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Data are expressed as mean±SEM.

*P<.01 vs baseline; †P<.01 vs atorvastatin and irbesartan alone.
betical complications and in acute endothelial dysfunction.\textsuperscript{28} Convincingly, free fatty acids may work the same way\textsuperscript{16}: free fatty acids increase oxidative stress generation in humans and induce endothelial dysfunction, which can be reversed by antioxidants.\textsuperscript{30} The increase in NT, a useful marker of both peroxynitrite and NO activity, during hyperglycemia or fat load supports this hypothesis.\textsuperscript{13–15} However, superoxide generation at the mitochondrial level is probably only the first, perhaps the most important, source of free radicals in the conditions described above.

Many other pathways, including NF-$\kappa$B, protein kinase C, and NADPH, are activated during hyperglycemia and lipid overload.\textsuperscript{16,20} Superoxide generated by NADPH seems to be of particular interest in the atherosclerotic process.\textsuperscript{31} NF-$\kappa$B modulates NADPH activity and genes involved in the generation of inflammation and is activated in vivo during acute hyperglycemia or free fatty acid overload.\textsuperscript{32,33} Similarly, protein kinase C modulates NADPH, particularly in presence of high glucose, stable or oscillating, and free fatty acids.\textsuperscript{34,35}

Statins and AT-1 receptor inhibitors work as antioxidant in different ways. Blocking the enzyme HMG-CoA reductase, statins inhibit the synthesis of mevalonic acid, a precursor of many nonsteroidal isoprenoid compounds, and cholesterol biosynthesis.\textsuperscript{18} The intermediate compounds are responsible for the intracellular trafficking of several membrane-bound proteins like Rho and Ras GTPase, which modulate NADPH activity.\textsuperscript{18} Interestingly, atorvastatin has been shown to reduce NADPH-mediated superoxide generation in endothelial cells exposed to high glucose.\textsuperscript{36}

AT-1 receptor blockers also modulate NADPH activity; this is particularly true in the presence of high glucose.\textsuperscript{37,38} However, the effect is obviously due to the blockade of the specific receptor, which favors the translocation of Ral-induced NADPH overexpression.\textsuperscript{37} Interestingly, in vitro, statins attenuate angiotensin II–induced free radical production, also downregulating AT-1 receptor expression,\textsuperscript{39} whereas Wassmann et al\textsuperscript{40} found in vivo that angiotensin II–induced reactive oxygen species were significantly reduced in rats treated with atorvastatin. These data suggest that in cells the pro-oxidant/antioxidant pathways regulated by AT-1 receptor blockers and statins are in a strict interplay.

Statins and AT-1 receptor blockers have been shown singularly to reduce NT generation in diabetic patients, even during an acute increase in glycemia.\textsuperscript{13,15,17} Because they work through different ways, it seems true that by combining the 2 compounds the effect on oxidative stress can be amplified, as demonstrated by our data.

On the other hand, evidence for the possibility of obtaining a more marked effect on endothelial dysfunction, inflammation, and oxidative stress by combining statins with the inhibition of angiotensin II system or blocking AT-1 recep-
Figure 4. Effects of short-term atorvastatin, irbesartan, and their combination on endothelial dysfunction, oxidative stress, and inflammation induced during oral glucose tolerance test plus high-fat load in diabetic patients. Bars indicate SEM.

Recent evidence suggests that statins may ameliorate endothelial function independently of their lipid-lowering effect, even during short-term treatment. At the same time, the protective effect of acute AT-1 receptor blockers on endothelial dysfunction has also been described. Our data provide evidence for the efficacy of both statins and AT-1 receptor blockers during short-term administration.

In conclusion, our data confirm that in diabetic patients postprandial hyperglycemia and hypertriglyceridemia have a damaging effect on endothelial function, producing oxidative stress and inflammation. They also show that short-term treatment with atorvastatin and irbesartan may counterbalance this phenomenon, with the combination of the 2 compounds being more effective. It is noteworthy that all the studied parameters—endothelial dysfunction, NT-proBNP, C-reactive protein, IL-6, and ICAM-1—have been shown to be independent predictors of CVD. Because postprandial state is a risk factor for CVD even in diabetic patients, this finding may have relevance in the clinical effort in preventing CVD in diabetic patients.

References


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_Circulation_. 2005;111:2518-2524; originally published online May 2, 2005;
doi: 10.1161/01.CIR.0000165070.46111.9F
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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