Body Mass Index

A Risk Factor for Unstable Angina and Myocardial Infarction in Patients With Angiographically Confirmed Coronary Artery Disease

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Background—In patients with coronary artery disease (CAD), acute thrombosis frequently occurs in coronary arteries with only mild or moderate stenoses. Obesity increases the risk of atherosclerosis, but it is not known whether it also increases the risk of coronary thrombosis. We hypothesized that body mass index (BMI) might be an independent predictor of an acute coronary syndrome in patients with established coronary atherosclerosis.

Methods and Results—Of 504 patients undergoing coronary angiography, those with evidence of >10% coronary artery stenoses were divided into 2 groups, with either stable (n=226) or unstable CAD (unstable angina or myocardial infarction; n=156). After adjusting for other risk factors (age, gender, blood pressure, lipid levels, insulin resistance, leptin, fibrinogen, C-reactive protein (CRP), CAD severity on angiography, smoking status, and a history of myocardial infarction or hypertension), BMI had a significant independent association with an acute coronary syndrome, with an odds ratio of 1.49 (P=0.014). This positive relation between BMI and the risk of acute coronary events was evident for even mildly elevated BMI values. Multivariate analysis also showed that CRP and the number of coronary lesions were independent predictors of risk of an acute coronary event.

Conclusions—In patients with established coronary atherosclerosis, BMI, as well as CRP and number of coronary lesions, are independently associated with acute coronary syndromes. There is evidence of increased risk even at mildly elevated BMI levels. (Circulation. 2003;108:2206-2211.)

Key Words: obesity ■ coronary disease ■ atherosclerosis ■ angiography
BMI with that of both traditional and novel CAD risk factors.\textsuperscript{12,13}

**Methods**

All subjects were recruited prospectively in a cardiac catheterization laboratory at the Mayo Clinic, Rochester, Minn. The study group consisted of 504 consecutive patients who were undergoing coronary angiography for clinical indications (most frequently chest pain, dyspnea on exertion, or an abnormal nuclear imaging study). These patients were part of another study examining the association between polymorphisms in the IL-1 cluster of genes and the severity of inflammation and CAD.\textsuperscript{14}

The exclusion criteria were diabetes, smoking history >50 pack-years, history of organ transplantation, prior coronary revascularization, bleeding disorders, blood transfusion within 30 days, HIV infection, renal failure, prior chest radiation therapy, and pregnancy. Of the original 504 subjects, only those with coronary artery stenosis on angiography of >10% (n=382) were included in further analysis. These patients were subsequently divided into a subgroup with stable CAD (n=226) and a subgroup with an acute coronary syndrome (n=156). The subjects with an acute coronary syndrome had a final clinical diagnosis of unstable angina (n=116) or acute myocardial infarction (n=40). Patients were classified as having unstable angina if they had chest pain that was new in onset or if they had chest pain that was increased frequency, increased intensity, increased duration, or decreased response to nitrates in the previous 2 months. Patients were defined as having an acute myocardial infarction if they had cardiac marker elevation (total creatine kinase >3 times the upper limit of normal or cardiac troponin T more than the upper limit of normal) in association with chest pain or ischemic electrocardiographic changes. The classification of a patient as having unstable angina or acute myocardial infarction was done both prospectively at enrollment and retrospectively by review of the clinical histories of all patients, blinded to BMI and outcome.

Blood samples were drawn at rest in the supine position after an overnight fast. Insulin resistance was calculated by means of the homeostasis model assessment (HOMA).\textsuperscript{15}

Of the 226 patients with stable CAD, 31 (13.7%) were Olmsted County residents, and of the 156 patients with an acute coronary syndrome, 19 (12.2%) were Olmsted County residents. The demographic and clinical characteristics of the study groups are shown in Table 1. as are other measured variables including leptin, insulin, glucose, lipids, fibrinogen, and C-reactive protein (CRP). The two groups were compared to assess for any independent association between BMI and the risk of an acute coronary syndrome.

The study was approved by the Mayo Clinic Institutional Review Board.

**Statistical Analysis**

Continuous variables with little to mild skewness were summarized as mean±SD and compared by means of the Student t test. Continuous variables with skewed distributions were summarized as median (first, third quartile) and compared with the Wilcoxon rank-sum test. Discrete variables were represented as frequencies and group percentages. Nominal variables were tested with the Pearson \( \chi^2 \) test and ordinal variables were tested with the Wilcoxon rank-sum test. All tests were 2-tailed, with a 0.05 type I error rate. Logistic regression models were used to estimate odds ratios. Due to skewness, log transformations of high-sensitivity CRP, insulin resistance, triglycerides, and leptin were used. All continuous variables (except number of lesions ≥50% stenosis) were standardized in the models so that the presented odds ratio is for a 1-SD change in the variable. Continuous variables were inspected for deviations from linearity in the logistic model. Simple logistic regression models were used to estimate the unconditional odds ratios for unstable CAD. Multiple logistic regression models were used to

\begin{table}
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\small
\begin{tabular}{lccc}
\hline
 & Stable CAD (n=226) & Unstable CAD (n=156) & \( P \) \\
\hline
Age, y & 63.7±9.4 & 59.7±10.4 & <0.001 \\
Male, No. (%) & 152 (67%) & 114 (73%) & 0.22 \\
BMI, kg/m\(^2\) & 28.8±4.7 & 30.5±5.7 & 0.002 \\
Current smoker, No. (%) & 14 (6%) & 18 (12%) & 0.06 \\
Hypertension, No. (%) & 111 (49%) & 82 (53%) & 0.51 \\
Family history of CAD, No. (%) & 55 (24%) & 46 (29%) & 0.26 \\
Prior MI, No. (%) & 24 (11%) & 50 (32%) & <0.001 \\
Systolic pressure, mm Hg & 136±25 & 128±25 & 0.003 \\
Diastolic pressure, mm Hg & 72±12 & 72±11 & 0.92 \\
Mean pressure, mm Hg & 98±16 & 95±14 & 0.08 \\
Leptin, median (Q1, Q3), ng/mL & 9.9 (5.6, 19.1) & 8.3 (5.3, 17.1) & 0.53 \\
Insulin, median (Q1, Q3), \( \mu \)g/mL & 4.8 (3.4, 6.8) & 5.4 (3.7, 8.3) & 0.05 \\
Glucose, mg/dL & 89.7±11.7 & 92.1±17.3 & 0.11 \\
Insulin resistance, median (Q1, Q3) & 1.1 (0.7, 1.6) & 1.2 (0.8, 1.8) & 0.039 \\
Total cholesterol, mg/dL & 210±49 & 208±41 & 0.60 \\
LDL cholesterol, mg/dL & 126±38 & 129±38 & 0.55 \\
HDL cholesterol, mg/dL & 47±12 & 44±13 & 0.032 \\
TG, median (Q1, Q3), mg/dL & 156 (120, 217) & 158 (112, 219) & 0.79 \\
Fibrinogen, mg/dL & 448±115 & 492±139 & <0.001 \\
hsCRP, median (Q1, Q3), mg/dL & 0.2 (0.1, 0.5) & 0.4 (0.2, 1.2) & <0.001 \\
No. of coronary lesions ≥50% & 2.1±2.4 & 3.0±2.2 & <0.001 \\
No. of coronary lesions ≥70% & 1.3±1.8 & 2.0±1.7 & <0.001 \\
\hline
\end{tabular}
\caption{Demographic and Clinical Characteristics of Study Groups}
\end{table}
estimate the association between BMI and unstable CAD adjusted for age, gender, high-sensitivity CRP, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, smoking status, prior myocardial infarction, insulin resistance, fibrinogen, leptin, history of hypertension, and number of coronary lesions with a 50% reduction in luminal diameter (used as an index of CAD severity). BMI was analyzed both continuously and categorically, with BMI classes determined by the sample quintiles.

**Results**

Most of the traditional CAD risk factors (elevated CRP and fibrinogen, low HDL cholesterol, prior myocardial infarction, insulin resistance) had significant unconditional associations with unstable CAD (Table 2). Some risk factors had “protective” associations (age, systolic blood pressure). In multiple regression models, an acute coronary syndrome remained positively correlated with elevated CRP and negatively correlated with age (Table 3).

In multivariate but not univariate analysis, higher triglyceride levels and higher leptin levels were associated with a lower risk of an acute coronary syndrome (Tables 2 and 3). The protective effect of triglycerides in the multiple regression model appears to be a function of its multicollinearity with age, HDL cholesterol, and insulin resistance. A model with only these four variables produced a significantly protective effect for triglycerides. It is not clear, however, whether this is a statistical anomaly or whether it represents a real biological phenomenon.

There was strong evidence of a quadratic association between the number of coronary lesions and unstable CAD (both in univariate and multivariate analysis). In fact, of any of the variables, the number of significant coronary lesions had the strongest association with unstable CAD, with the highest risk occurring around 4 or 5 lesions (Tables 2 and 3).

BMI (analyzed as a continuous variable) was positively correlated with the presence of an acute coronary syndrome in univariate analysis, with an odds ratio of 1.40 for every 1-SD (5.18 kg/m²) increase in BMI (P = 0.002) (Table 2). After adjusting for all other risk factors (including CRP and number of significant coronary lesions), BMI was still associated with unstable CAD (Table 3). Specifically, every 1 SD of increase in BMI resulted in a 49% increase in odds of unstable angina or myocardial infarction (P = 0.014). To demonstrate the relation indicated by the multiple regression model, odds ratios and 95% confidence intervals were calculated for different BMI values, with BMI = 20 set as the reference point (Figure). There was no evidence that polynomial BMI terms would add significant information to the model.

BMI was also analyzed as a categorical variable split by quintiles (data not shown). The results were similar. Most important, this analysis indicated that patients with even mildly elevated BMI (25.6 to 27.6) had a significantly greater risk of an unstable coronary syndrome than those with normal BMI (<25.6).

**Discussion**

The novel and important finding of the present study is that increased BMI is associated with a greater risk of an acute coronary syndrome (either unstable angina or myocardial infarction) in patients with angiographically confirmed coronary atherosclerosis. Since all stable control patients also had
CAD, our study has the potential to separate the risks of plaque rupture and thrombosis (i.e., the pathology believed to underlie unstable angina and myocardial infarction) from the risk factors for atherosclerosis. The positive relation between BMI and the risk of acute coronary events was present even in the range of normal or only mildly elevated BMI. Furthermore, the effect of BMI was independent of many other metabolic and cardiovascular risk factors, such as age, gender, blood pressure, lipid levels, insulin resistance, leptin, fibrinogen, CRP, CAD severity on angiography, smoking status, history of myocardial infarction, or hypertension. In fact, in a multiple regression model, the only variables positively correlated with unstable CAD were BMI, CRP, and the number of significant coronary lesions on angiography.

The observation of the independent correlation between BMI and the odds for unstable CAD is important and of interest. Obesity is part of the metabolic syndrome (which also includes hypertension, dyslipidemia, insulin resistance, and systemic inflammation) and causes a clustering of these risk factors. Our data suggest that the increased risk of unstable CAD imparted by high BMI is not explained by the normal obesity-related risk factors or by the traditional definition of the metabolic syndrome and may therefore be related to other effects of increased body mass, some of which will be discussed below.

Acute coronary events are initiated by a rupture of an atheromatous plaque. Plaque stability and the balance between prothrombotic and antithrombotic bloodborne mediators are important in determining the susceptibility of an atheromatous coronary artery to the development of an occlusive intraluminal thrombus. The factors that make a plaque susceptible to rupture include, among others, decreased collagen synthesis, inflammation, and a large lipid pool with increased cholesterol content in the plaque.16

The mechanisms underlying the association between increased BMI and CAD instability (as found in the present study) are essentially unknown. Some theoretical explanations should be considered. Obesity, acting through hyperlipidemia and inflammation,17 may increase vulnerability of the atheromatous plaque to rupture. However, in our study, the effect of BMI on the risk of unstable CAD was independent of plasma lipid levels and CRP. Obesity has also been associated with increased expression of tissue factor,18 enhanced platelet activation,19 and elevated plasminogen activator inhibitor-1 (PAI-1).20 and may hence affect the initiation and progression of intraluminal thrombosis after coronary plaque rupture. Finally, obesity may be associated with cardiac hypertrophy21 and may impair coronary flow reserve, increasing the likelihood of myocardial ischemia. Alternatively, hitherto unidentified and novel obesity-

### Table 3. Multiple Logistic Regression Estimates for Presence of Unstable CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.49</td>
<td>1.08</td>
<td>2.06</td>
<td>0.014</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.63</td>
<td>0.48</td>
<td>0.83</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.55</td>
<td>0.25</td>
<td>1.21</td>
<td>0.14</td>
</tr>
<tr>
<td>Log(CRP)</td>
<td>1.72</td>
<td>1.25</td>
<td>2.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>0.90</td>
<td>0.68</td>
<td>1.18</td>
<td>0.43</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.00</td>
<td>0.75</td>
<td>1.32</td>
<td>0.97</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.90</td>
<td>0.71</td>
<td>1.15</td>
<td>0.40</td>
</tr>
<tr>
<td>Log(TG)</td>
<td>0.76</td>
<td>0.59</td>
<td>0.98</td>
<td>0.032</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.26</td>
<td>0.50</td>
<td>3.16</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.72</td>
<td>0.89</td>
<td>3.33</td>
<td>0.11</td>
</tr>
<tr>
<td>Log (insulin resistance)</td>
<td>1.11</td>
<td>0.82</td>
<td>1.51</td>
<td>0.49</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.02</td>
<td>0.74</td>
<td>1.39</td>
<td>0.93</td>
</tr>
<tr>
<td>Log(leptin)</td>
<td>0.65</td>
<td>0.43</td>
<td>1.00</td>
<td>0.049</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.26</td>
<td>0.77</td>
<td>2.07</td>
<td>0.36</td>
</tr>
<tr>
<td>No. of coronary lesions &gt;=50%*</td>
<td>1.96</td>
<td>1.46</td>
<td>2.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Linear</td>
<td>0.94</td>
<td>0.90</td>
<td>0.97</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Quadratic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TG indicates triglycerides; MI, myocardial infarction.
*Not standardized for analysis

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Adapted from [Wolk et al.](http://circ.ahajournals.org/)

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**Odds Ratio**

- **BMI (kg/m²)**
  - Adjusted odds ratios for unstable CAD for BMI range of 20 to 40 kg/m². Vertical bars denote 95% CIs.
dependent mechanisms may contribute to the observed association between BMI and risk for CAD instability. Understanding these mechanisms may provide opportunities for new and targeted therapeutic strategies.

Other independent and important predictors of coronary artery disease instability in the present study include elevated levels of CRP as well as the number of significant coronary artery lesions. Rapid lowering of CRP, perhaps by the use of statins, aspirin, or other agents, may therefore contribute to coronary artery disease stability and may help explain the very early benefit of statins in attenuating coronary ischemic syndromes even during hospitalization or after a few weeks’ treatment, before effects of lipid lowering would be expected to be manifest.

In multivariate analysis, leptin was found to have an independent protective association with unstable CAD (Table 3). The actual mechanisms of this effect of leptin are not known and require further investigation. Possible explanations are the proangiogenic action of leptin, coronary artery vasodilation, and activation of endothelial nitric oxide production, which may improve blood supply to the myocardium and decrease ischemia despite the presence of CAD. This inverse relation between leptin and CAD instability in patients with CAD who are undergoing cardiac catheterization contrasts with the longer-term effects of hyperleptinemia as a possible predictor of cardiovascular events.

Study Limitations

One potential study limitation is the possibility of recruitment bias, such that obese subjects with coronary symptoms would be more likely to undergo angiography. We believe, however, that this is unlikely for the following reasons. First, in our study, well over 90% of eligible patients undergoing coronary angiography during the study period were included, and by far the most common reason for exclusion was patient refusal to participate in the study. Second, our institutional guidelines for referral for angiography and the practice patterns of our physicians do not reflect that weight has an influence on whether or not to proceed with coronary angiography. Third, potential effects of referral bias were decreased in our study by excluding patients with diabetes, significant smoking history, prior revascularization, prior radiation to the chest, and renal failure, because the presence of these conditions (all associated with an increased risk of CAD) might influence clinical judgment and the threshold for angiography. Fourth, we excluded patients with diabetes, the majority of whom have obesity-related type 2 diabetes. Exclusion of patients with diabetes (who are more obese and at increased risk of CAD) might decrease rather than increase the number of obese subjects in our unstable CAD group. Last, we found that CRP was also an independent and powerful predictor of likelihood of an acute coronary syndrome. This latter finding is consistent with what has been proposed earlier in the literature for CRP in association with CAD instability and is consistent with the expected pathophysiologic actions of CRP. Therefore our results speak to the validity of the identification of our study population and hence the validity of our finding of BMI as an important and independent predictor of the likelihood of an acute coronary syndrome. As with any novel finding, these data will need to be confirmed in subsequent studies by other investigators and in other patient populations.

Another limitation is that our study does not identify the specific mechanism/s mediating the BMI effect on risk for acute coronary syndromes. Nevertheless, we included a very broad spectrum of traditional and novel risk factors for acute cardiovascular events. What is important is that none of these acknowledged risk mediators can explain the increased risk associated with BMI, suggesting that there are other unrecognized mechanisms, through which even modest increases in body mass would contribute to increased cardiovascular risk. Our findings therefore go beyond the current mechanistic understanding of the obesity syndrome and suggest that mechanisms other than the normal obesity-related risk factors need to be invoked to explain the increased risk of unstable CAD imparted by high BMI.

Conclusions

Increased BMI, as well as CRP and the number of coronary artery lesions, are each independently associated with acute coronary syndromes, in that they increase the likelihood of unstable angina or myocardial infarction in patients with established CAD. These effects are independent of other traditional metabolic and cardiovascular risk factors, including those directly related to obesity, such as insulin resistance and dyslipidemia. In patients with established atherosclerosis, even “normal” and mildly elevated BMI is associated with the risk of unstable CAD. These findings may have important implications both for understanding the decreased life expectancy associated with obesity as well as for the clinical management of patients with coronary atherosclerosis.

Acknowledgments

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References

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