Relationship Between Insulin Resistance and Partially Oxidized LDL Particles in Healthy, Nondiabetic Volunteers

Marcello Carontoni, Fahim Abbasi, Fabienne Warmerdam, Mark Klebanov, Pei-Wen Wang, Yii-Der I. Chen, Salman Azhar, Gerald M. Reaven

Abstract—This study was performed in 36 healthy volunteers to define the relationship between plasma concentrations of partially oxidized low density lipoprotein (poxLDL), plasma glucose and insulin responses to oral glucose, and steady-state plasma glucose (SSPG) concentrations after a 180-minute infusion of somatostatin, insulin, and glucose. The concentration of poxLDL was estimated by determining the amount of conjugated dienes formed during in vitro LDL oxidation in the presence or absence of alanine. Under these conditions, the greater the in vitro antioxidant effect of alanine, the lower the amount of poxLDL that was present in plasma. The results demonstrated that plasma poxLDL concentration was significantly correlated with plasma glucose (r=.53, P<.001) and insulin (r=.43, P<.01) responses, SSPG concentrations (r=.53, P<.001), and plasma triglyceride (r=.42, P<.01) and HDL cholesterol (r=-.50, P<.002) concentrations. Furthermore, these relationships persisted when the data were corrected for differences in age, sex, body mass index, and the ratio of waist to hip girth. Of note, there was no correlation between poxLDL and LDL cholesterol concentration. When SSPG was entered along with age, sex, body mass index, and waist-to-hip ratio in a multiple regression model, SSPG alone was a significant prediction of poxLDL (r²=.37, P<.02). The addition of plasma glucose and insulin responses and triglyceride and HDL cholesterol concentrations increased the r² to only .47. These results show that the amount of poxLDL in plasma is significantly correlated with insulin resistance (ie, SSPG) and its metabolic consequences. (Arterioscler Thromb Vasc Biol. 1998;18:762-767.)

Key Words: oxidized LDL ■ insulin resistance ■ cardiovascular disease risk factors

Previous reports from our laboratory have emphasized the potential link between insulin resistance, a cluster of associated abnormalities, and atherosclerosis in nondiabetic subjects. An important component of the metabolic abnormalities associated with insulin resistance is a change in LDL particle diameter, leading to the presence of smaller and denser LDL particles. Given the fact that such particles are more easily oxidized, it seemed to be of great interest to know whether there were any associations between insulin resistance and the oxidative states of circulating LDL. Approaching this problem is complicated by the fact that oxLDL has been detected in the arterial wall, but not in the circulation. LDL oxidation has usually been assessed by determining the formation of thiobarbituric acid–reactive compounds or by the lag time for conjugated-diene formation during copper oxidation—methods that do not permit determination of the oxidized state of LDL present in the circulation. In an effort to overcome this problem, Picard et al7 used this method to show that LDL oxidation was increased in patients with type 2 diabetes who had evidence of atherosclerosis but absent in diabetic subjects with no apparent vascular disease. Since there is increasing evidence1,2,4 that insulin resistance or compensatory hyperinsulinemia is associated with a variety of CHD risk factors, we initiated the current study to see whether there was any relationship between the resistance of insulin-mediated glucose disposal or the metabolic variables associated with insulin resistance and the amount of poxLDL in nondiabetic volunteers, all of whom were in general good health.

Methods

The study population consisted of 36 healthy volunteers, 14 men and 22 women, who responded to a newspaper advertisement indicating our interest in studying factors that modulate insulin action and CHD risk factors in healthy volunteers. Their mean age (±SD) was 55±11 years. The individuals selected for study were defined as healthy on the basis of medical history, physical examination, and normal results from routine laboratory tests and electrocardiography and because they were found to be nondiabetic after a 75-g oral glucose load. No subject was a smoker, nor was any subject taking any drugs...
known to affect glucose or insulin metabolism. The study protocol was approved by the Stanford University Institutional Review Board, and written, informed consent was obtained from all subjects.

All studies were performed at the General Clinical Research Center of Stanford University Medical Center after an overnight fast. The degree of obesity, overall and regional, was estimated by BMI and WHR, respectively. Venous blood was used for measurement of plasma cholesterol, triglyceride, and HDL cholesterol concentrations. Plasma glucose and insulin concentrations were determined before and at 30, 60, 90, 120, and 180 minutes after oral administration of 75 g glucose. The total integrated area of the plasma concentrations during this 180-minute period was used to quantify plasma glucose and insulin responses. The ability of insulin to promote glucose uptake was estimated by a modification of the insulin suppression test as validated by our laboratory. After an overnight fast, an intravenous catheter was placed in each of the patient’s arms. Blood was sampled from one arm for measurement of plasma cholesterol and insulin concentrations, and the contralateral arm was used for administration of test substances. Somatostatin was administered (250 μg/h in a solution containing 2.5% (wt/vol) human serum albumin) to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at rates of 25 mU · m⁻² · min⁻¹ and 240 mg · m⁻² · min⁻¹, respectively. Blood was sampled every 0.5 hour until 150 minutes had elapsed and then every 10 minutes until 180 minutes had elapsed. The four values obtained at 150, 160, 170, and 180 minutes were averaged and considered to represent the SSPG and SSPI concentrations achieved during the infusion. Because SSPI concentrations are similar in all individuals, SSPG concentrations provide a direct estimate of insulin-mediated glucose disposal in each individual: the lower the SSPG, the more insulin suppression test as validated by our laboratory. After an overnight fast, an intravenous catheter was placed in each of the patient’s arms. Blood was sampled from one arm for measurement of plasma cholesterol and insulin concentrations, and the contralateral arm was used for administration of test substances. Somatostatin was administered (250 μg/h in a solution containing 2.5% (wt/vol) human serum albumin) to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at rates of 25 mU · m⁻² · min⁻¹ and 240 mg · m⁻² · min⁻¹, respectively. Blood was sampled every 0.5 hour until 150 minutes had elapsed and then every 10 minutes until 180 minutes had elapsed. The four values obtained at 150, 160, 170, and 180 minutes were averaged and considered to represent the SSPG and SSPI concentrations achieved during the infusion. Because SSPI concentrations are similar in all individuals, SSPG concentrations provide a direct estimate of insulin-mediated glucose disposal in each individual: the lower the SSPG, the more insulin sensitive the individual.

An aliquot of fasting venous blood (20 mL) was drawn from each individual into EDTA tubes and immediately centrifuged. Plasma was flushed with N₂ and stored frozen at −70°C until assayed. LDLs (d=1.025 to 1.063 g/mL) were isolated by sequential ultracentrifugation using solid KBr for density adjustment. All plasma samples were supplemented with protease inhibitors (0.1 mmol/L PMSF and 2 μg/mL aprotinin) to minimize LDL degradation during isolation. The LDL preparations were dialyzed against PBS without EDTA and containing Chelex-100 (1 g/L). After addition of EDTA to a final concentration of 0.5 mmol/L, the dialyzed LDL preparations were partially oxidized LDLs (10 mg total cholesterol per milliliter) were stored at −20°C for up to 1 week. These results are shown in Fig 2, which reveals a mean (±SD) difference between the two estimates of [1 ± 6.3 (P<.68 by Student’s paired t test)]. In addition, in 10 samples we compared the value of cAOC with (1) the lag phase after the addition of copper before any change in absorbance (r=.66, P<.05), (2) the maximum CD formation (r=.64, P<.01), and (3) total lipid.

**Figure 1.** Definition of cAOC. AOC is a function of the ability of alanine to modify CD formation during copper oxidation and is defined as (Th1−Th0)×100/Th0; cAOC=150−AOC. AOC is higher to the degree that LDL was oxidized prior to copper oxidation. Th indicates half-time of CD formation; Th0, half-time of CD formation in the absence of alanine; and Th1, half-time of CD formation in the presence of alanine.

As reported by Picard et al, the increase in CD formation half-time induced by alanine can be expressed as the AOC, which can be calculated as (Th1−Th0)×100/Th0, ie, the percentage increase due to alanine. As AOC is inversely correlated with the degree of LDL oxidation, Picard et al expressed their results as the cAOC, which is equal to 150−AOC (based on their experience that the value of AOC never exceeded 150%). The cAOC thus varies in direct proportion to the degree of LDL oxidation. We also calculated cAOC, but for clarity of presentation, will refer to this value as the amount of partially oxidized LDL, or poxLDL. Finally, to estimate the reproducibility of the results, we measured cAOC on the same isolated LDL sample from 7 subjects. For this purpose, isolated LDL preparations (10 mg total cholesterol per milliliter) were stored at 4°C under sterile conditions and in the presence of 0.5 mmol/L EDTA (pH 7.0). Contaminating metal ions were removed from LDL preparations by dialysis against PBS without calcium or magnesium and containing Chelex-100 (1 g/L). After addition of EDTA to a final concentration of 0.5 mmol/L, the dialyzed LDL preparations were filtered (Millipore, 0.2-μm filter), flushed with N₂, and stored in the dark at 4°C for up to 2 months. These results are shown in Fig 2, revealing a mean (±SD) difference between the two estimates of [1 ± 6.3 (P<.68 by Student’s paired t test)]. In addition, in 10 samples we compared the value of cAOC with (1) the lag phase after the addition of copper before any change in absorbance (r=.66, P<.05), (2) the maximum CD formation (r=.64, P<.01), and (3) total lipid.

**Figure 2.** Plasma poxLDL in 7 volunteers when measured in two separate aliquots, before and after freezing at −20°C for 2 months.
peroxide formation at 100 minutes \((r = .61, P < .05)\). Furthermore, the SSPG in these 10 samples was also highly correlated with all four measurements: cAOC \((r = .82, P < .01)\), lag phase \((r = .89, P < .001)\), CD \((r = .78, P < .01)\), and lipid peroxides \((r = .68, P < .05)\).

Data were stored and analyzed using the Systat 6.0 package for Windows. Insulin response and plasma triglyceride values were logarithmically transformed to improve normality for statistical testing and back-transformed for presentation in tables. Pearson product-moment correlations and partial correlation coefficients were calculated to determine relations between variables of interest. Finally, multiple regression analysis was performed using different models (see “Results”) with the dependent variable being cAOC.

### Results

Baseline characteristics of the 36 normal volunteers are given in Table 1. It can be seen from these data that they represented a broad range in terms of both their demographic and metabolic values. Table 2 shows the relationships between the estimated degree of LDL oxidation (ie, poxLDL) and several metabolic variables. These data demonstrate the presence of significant simple correlation coefficients between poxLDL and SSPG \((r = .52; P < .001)\) and plasma glucose and insulin responses to a 75-g oral glucose load \((r = .53\) and \(r = .43\); respectively \(P < .001\) and \(P < .01\)). These results are also displayed as a scattergram in Fig 3. LDL oxidation status was also positively correlated with plasma triglyceride \((r = .42, P < .01)\) and negatively with HDL cholesterol concentrations \((r = -.50, P < .002)\). However, no significant relationship was detected between poxLDL and either total or LDL cholesterol concentrations. Because the volunteers varied in terms of age, sex, BMI, and WHR, the correlation coefficients were adjusted for these four variables, and these results are also shown in Table 2. When this was done, SSPG concentration, glucose and insulin response to oral glucose, and triglyceride concentration still remained significantly correlated, whereas the relationship between poxLDL and HDL cholesterol concentration became marginally significant.

### Table 1. Clinical and Metabolic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±2</td>
<td>34–75</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>14/22</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±0.6</td>
<td>20–33</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84±0.01</td>
<td>0.67–0.97</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.4±0.1</td>
<td>3.3–7.7</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>89±8</td>
<td>31–199</td>
</tr>
<tr>
<td>Glucose response, mmol · L⁻¹ · 3 h⁻¹</td>
<td>19.9±0.8</td>
<td>11.9±33.3</td>
</tr>
<tr>
<td>Insulin response, pmol · L⁻¹ · 3 h⁻¹</td>
<td>1305.3±159.5</td>
<td>409–5155.2</td>
</tr>
<tr>
<td>SSPG, mmol/L</td>
<td>7.7±0.6</td>
<td>2.9–15.4</td>
</tr>
<tr>
<td>SSPI, pmol/L</td>
<td>421±23</td>
<td>288–626</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.1±0.2</td>
<td>2.4–7.7</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.5±0.2</td>
<td>0.5–7.4</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1±0.06</td>
<td>0.7–2.2</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.2±0.2</td>
<td>0.9–6.2</td>
</tr>
<tr>
<td>poxLDL (cAOC)</td>
<td>113.6±2.5</td>
<td>77–139</td>
</tr>
</tbody>
</table>

Values are mean±SEM except for age, which is reported as mean±SD.

### Table 2. Correlation Coefficients Between poxLDL and Insulin Resistance and Plasma Glucose, Insulin, and Lipid Concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simple Coefficients, (r (P))</th>
<th>Partial Coefficients, (r (P))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose response</td>
<td>.53 (&lt;.001)</td>
<td>.46 (&lt;.006)</td>
</tr>
<tr>
<td>Insulin response</td>
<td>.43 (&lt;.009)</td>
<td>.36 (&lt;.04)</td>
</tr>
<tr>
<td>SSPG</td>
<td>.52 (&lt;.001)</td>
<td>.41 (&lt;.02)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>.07 (NS)</td>
<td>-.05 (NS)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>.42 (&lt;.01)</td>
<td>.35 (&lt;.05)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-.50 (&lt;.002)</td>
<td>-.31 (&lt;.08)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>.03 (NS)</td>
<td>-.1 (NS)</td>
</tr>
</tbody>
</table>

*Correlation coefficients were adjusted for age, sex, BMI, and WHR.

Figure 3. Relationship between poxLDL and plasma glucose response (top), plasma insulin response (middle), and SSPG concentration (bottom).
Both overall and abdominal obesity\textsuperscript{16} have been said to increase LDL oxidizability. In addition, age may\textsuperscript{17} or may not\textsuperscript{18} have this same effect. Consequently, we performed multiple regression analysis to determine whether any of these factors could affect LDL oxidation status independently of insulin resistance or its metabolic covariates. The data reported in Table 3 show that SSPG (\(P<.02\)) but neither age, BMI, nor WHR was independently related to poxLDL (for the entire model, \(r^2=.37\)). We obtained similar results (data not shown) when SSPG was replaced with either plasma glucose (\(r^2=.41, P<.005\)) or insulin response (\(r^2=.34, P<.04\)), triglyceride (\(r^2=.33, P<.05\)) or HDL cholesterol (\(r^2=.31, P<.08\)).

When insulin resistance and all of its metabolic covariates were forced into the model together, they all lost independent predictive power, highlighting the close relationship among these variables. Furthermore, the predictive value of the model including all variables (\(r^2=.47\)) was only marginally higher than the value of the model shown in Table 3 with SSPG as the only variable.

### Discussion

A major difficulty in assessing the role of oxLDL in atherogenesis is the fact that it is unlikely to be present as such in the plasma, and methods have not been available to assess in vivo the amount of poxLDL in the circulation. The ability to circumvent this problem became available with the recent publication by Picard and associates,\textsuperscript{2} who described a sensitive and reproducible method to estimate the amount of poxLDL in plasma. Their approach is based on the use of alanine to modify CD formation by isolated LDL, ie, the more the increase in CD formation due to alanine, the lesser the degree of LDL oxidation. We have used this approach in the current study, and it seems most appropriate to begin by addressing the utility of the method used in our attempt to estimate the degree to which circulating LDL was oxidized.

We believe the theoretical basis of the method to be reasonable, and the results of Picard et al\textsuperscript{1} and our data as shown in Fig 2 indicate that it is reproducible. Furthermore, the technique seems to be measuring something of biological interest. Thus, Picard et al\textsuperscript{1} showed that their new method differentiated between diabetic patients with and without evidence of clinical atherosclerosis. In the current study, we have described a significant and independent correlation between insulin resistance or compensatory hyperinsulinemia and the amount of poxLDL. It should be emphasized that the plasma LDL concentration, which is not related to insulin resistance,\textsuperscript{19} was not correlated with poxLDL. Consequently, there is at least some degree of specificity related to this measurement.

On the other hand, it is equally important to emphasize that we cannot ascribe any biological effect to the measurement of what we are designating as poxLDL. In fact, we have used the phrase “partially oxidized LDL” in this article in contrast to “minimally oxidized LDL” as employed by Picard et al\textsuperscript{2} to avoid any inference that what is measured corresponds to the in vitro biological effects of minimally oxidized LDL as described by Fogelman and colleagues.\textsuperscript{20–22}

In addition to using a method to estimate circulating levels of poxLDL rather than one based on measurements of the degree to which isolated LDL is oxidized in vitro, the other striking difference between our study and the majority of previous reports was that our experimental population was healthy, nondiabetic, without clinical signs of CHD, and with normal electrocardiograms. As such, our population differed considerably from previous studies that have demonstrated an increase in susceptibility of LDL to oxidation in patients with known CHD, either with or without diabetes.\textsuperscript{23–26} Indeed, we are aware of only two studies in which increases in LDL oxidizability have been shown to occur in subjects without vascular disease.\textsuperscript{16,27} In this context, the results of Haffner et al\textsuperscript{28} are most at odds with ours. These authors compared normal individuals, subjects with impaired glucose tolerance, and patients with frank non–insulin-dependent diabetes mellitus and concluded that in vitro LDL oxidizability was increased only in patients with non–insulin-dependent diabetes mellitus. They reasoned that since resistance to insulin-mediated glucose disposal is commonly seen in patients with impaired glucose tolerance or non–insulin-dependent diabetes mellitus, hyperglycemia but not insulin resistance was associated with enhanced LDL oxidizability. Although we cannot fault their logic, it is apparent that we observed a significant relationship between insulin resistance and poxLDL levels in a group of nondiabetic patients. It should be noted that neither Stringer et al\textsuperscript{29} nor Velázquez and associates,\textsuperscript{30} using an assay method similar to that of Haffner et al, were able to discern any effect of either diabetes or degree of hyperglycemia on LDL oxidizability in patients with atherosclerosis. In addition, Velázquez et al\textsuperscript{30} reported that in vitro LDL oxidation was elevated to a comparable degree in diabetic and nondiabetic subjects with CHD when compared with normal volunteers, and these authors were unable to define an independent relationship between estimates of glycemia and in vitro LDL oxidizability. The fact that neither of these latter two research groups was able to discern any relationship between plasma glucose concentration and LDL oxidizability suggests that LDL glycation is not the major mediator of changes in LDL oxidizability. This conclusion is further supported by the fact that the differences in poxLDL described in the current study were seen in nondiabetic volunteers. On the other hand, although the values were all within the normal range, there was a significant relationship noted in Table 2 between the plasma glucose response to oral glucose and poxLDL. Thus, we cannot exclude the possibility that there were changes in LDL glycation, secondary to minor variations in plasma glucose concentration within this nondi-

### Table 3. Multiple Regression Analysis of the Relationship Between poxLDL and Age, Sex, BMI, WHR, and Insulin Resistance

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.050</td>
<td>.22</td>
<td>.82</td>
</tr>
<tr>
<td>Sex</td>
<td>−8.553</td>
<td>7.93</td>
<td>.29</td>
</tr>
<tr>
<td>BMI</td>
<td>1.117</td>
<td>.86</td>
<td>.20</td>
</tr>
<tr>
<td>WHR</td>
<td>−13.060</td>
<td>52.66</td>
<td>.80</td>
</tr>
<tr>
<td>SSPG</td>
<td>1.920</td>
<td>.77</td>
<td>.018</td>
</tr>
</tbody>
</table>

*\(r^2\) for the entire model, .37.
abietic population, that contributed to the increase in poxLDL seen in insulin-resistant individuals.

If we now focus on nondiabetic individuals without clinical evidence of atherosclerosis, we are aware of only one publication other than ours that claims to have shown any change in LDL oxidation. More specifically, in a recent review, Van Gaal and colleagues presented evidence that in vivo oxidizability of a non-HDL fraction was increased in postmenopausal, obese women compared with a matched group of nonobese women and that this relationship was related to both BMI and WHR. Since insulin resistance is commonly seen in obese individuals, it is likely that this defect was also present in the obese women studied by Van Gaal et al. It is apparent from our results that the positive relationship between SSPG (insulin resistance) and poxLDL was independent of differences in sex, BMI, and WHR. Based on these considerations, it seems entirely possible that the changes in vivo LDL oxidizability described by Van Gaal et al in obese women were secondary to the insulin resistance in these individuals. As such, their results are quite consistent with ours.

If we now turn attention to our results, it is apparent from Table 2 that there were significant relationships between poxLDL and the other variables known to be associated with insulin resistance, ie, the plasma glucose and insulin responses to oral glucose, higher plasma triglyceride concentrations, and lower levels of HDL cholesterol. Furthermore, these relationships persisted after adjustment for differences in age, sex, BMI, and WHR, with only HDL cholesterol losing statistical power. As such, the amount of circulating poxLDL in the healthy volunteers we studied was related to all of the components of syndrome X. When a series of variables is related to the biological event being studied, multivariate analysis is conventionally used in an effort to define the independent predictors of the phenomenon in question. An example of this approach is seen in Table 3. When age, weight, sex, and SSPG (insulin resistance) were entered into the regression model, SSPG accounted for 36% of the variability of poxLDL and was the only statistically significant predictor. Essentially similar results were seen when insulin response, a surrogate measure of insulin resistance, replaced SSPG in the model. However, when all of the metabolic abnormalities associated with syndrome X were added to the model, the $r^2$ value increased from .36 to only .46, and none of the variables were found to be independent predictors of poxLDL. We believe that this finding reinforces the notion of a cluster of risk factors for CHD that are closely related to insulin resistance and suggest that statistical efforts to define independence may not be overly useful. Indeed, we believe that the point to emphasize is that the degree of insulin resistance per se accounted for 36% of the amount of variability in the circulating poxLDL level in a group of healthy volunteers.

Finally, though not the goal of this study, some speculation as to the link between the components of syndrome X and LDL oxidative states seems warranted. For example, Galvan et al have recently raised the possibility of a pro-oxidant action of insulin in vivo by demonstrating a consistent decrement in plasma vitamin E concentrations, a major free radical-scavenger molecule, during physiological hyperinsulinemia. Furthermore, Rifici et al were able to demonstrate that supraphysiological insulin concentrations may induce in vitro LDL oxidation by peripheral blood mononuclear cells and that this effect was mediated by an increase in $O_2$. Raised plasma glucose levels may also induce glycosylation of LDLs, and this effect has been demonstrated to increase LDL susceptibility to oxidation. It has also been hypothesized that normal to elevated HDL cholesterol concentrations may protect LDLs from oxidation by acting as a “scavenger” system for circulating lipoperoxides. Finally, it should be pointed out that the positive relationship between insulin resistance and poxLDL was seen in this study, despite the presumptive protective effect of the higher uric acid concentrations that are characteristic of subjects with syndrome X. Thus, there appear to be several potential means by which the various components of syndrome X could modify LDL oxidative status.

In conclusion, we have demonstrated in healthy volunteers that poxLDL concentrations are correlated with resistance to insulin-mediated glucose uptake, increased glucose and insulin responses to oral glucose, higher plasma triglyceride levels, and lower HDL cholesterol concentrations. These data suggest that an increase in LDL oxidative status should be added to the list of metabolic changes related to syndrome X. How insulin resistance or its consequences increase LDL oxidation in vivo is still unclear and requires further investigation. Nonetheless, these relations may well contribute to the increased risk of CHD that has been previously shown to be linked to insulin resistance and compensatory hyperinsulinemia.

Acknowledgments

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32. Carantoni et al. May 1998 767


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