Oxidation, Type 2 Diabetes and Coronary Heart Disease, a Complex Interaction. Findings from a Population-based Study

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**Objective:** We analyzed the interrelationship among oxidation, myocardial infarction (MI) and type 2 diabetes in a population-based case-control study of MI.

**Research Design and Methods:** Participants were 1,709 individuals from Western NY; 257 women and men with incident MI and 1,452 healthy controls (age 35-70 years). Lipid peroxidation was measured by plasma levels of thiobarbituric acid reactive substances (TBARS). History of type 2 diabetes was self report of medical diagnosis.

**Results:** In multivariate analyses, there was no significant difference in TBARS levels between cases and controls in both sexes. In sub-group analyses by diabetes status, diabetics, regardless of MI status, exhibited significantly higher TBARS values than non diabetics. In diabetic women: cases=1.84(nmol/ml), controls=1.83 (nmol/ml); in non diabetic women: cases=1.29(nmol/ml), controls=1.31(nmol/ml). In diabetic men: cases=1.65(nmol/ml), controls=1.97(nmol/ml); in non diabetic men: cases=1.36(nmol/ml), controls=1.36(nmol/ml).

**Conclusions:** While type 2 diabetes may be an important correlate of lipid peroxidation, clinical coronary heart disease may not.
Oxidation has been hypothesized as one of the plausible pathogenic mechanisms underlying the associations between coronary heart disease (CHD) and abnormalities in glucose and insulin metabolism (1). While several studies have demonstrated the presence of increased oxidative stress in either CHD or type 2 diabetes individually, very little is known about the interrelationship between oxidation, clinical atherosclerosis and type 2 diabetes in the general population. Thus, the current analysis attempts to examine this complex interaction using data from a population-based, case-control study of myocardial infarction (MI) among residents from two Western New York counties.

RESEARCH DESIGN AND METHODS

Data for the overall sample, identified as the Western New York Health Study, were collected between 1996 and 2001 (2-3). In all, 1,197 women and men, aged 35-70, discharged alive with a diagnosis of acute incident MI (4) [International Classification of Disease (ICD9=410)] were recruited from hospitals in Erie and Niagara Counties in New York State (75% of all the area hospitals). Control subjects were randomly selected among residents of Erie and Niagara Counties in the age range of 35-70 years. A total of 2,850 controls were interviewed, representing 59.5% of those identified and contacted and for whom we could determine eligibility. Biomarkers of lipid peroxidation were available for 3,615 individuals (969 cases, 2,646 controls) out of the total number of participants (n = 4,047: 1,197 cases/2,850 controls). The present study focuses on the 1,709 participants who were not taking statins or vitamins at the time of the interview (257 cases, 1,452 controls). This selection was done to avoid biochemical influences of these drugs on the oxidative status of participants.

All participants received a clinical examination that included resting blood pressure, measures of height, weight, and abdominal height. All participants were queried about their personal medical history, including physician diagnosis of hypertension, type 2 diabetes and hypercholesterolemia, and about a number of life-style habits, including dietary habits, alcohol consumption and personal smoking history. The reference time frame for questions regarding dietary and alcohol consumption habits was 12-24 months prior to the MI (for cases) or the interview (for controls). Hypertension, type 2 diabetes, hypercholesterolemia, and smoking status were assessed at the time of the MI (for cases) or the time of interview (for controls).

Blood was obtained by highly standardized protocols including uniform time of morning collection, fasting status of participants, phase of the menstrual cycle (for women) and activity prior to phlebotomy. The blood tubes used were immediately protected from light, kept at 4°C, processed and stored at -80°C within 90 minutes of collection. Thiobarbituric acid reacting substances (TBARS), triglycerides and glucose were measured using methods previously described (2, 5). Several quality control measures were implemented to maintain assay accuracy (2, 6).

We conducted two sets of ANOVA. In the first set, comparisons of adjusted TBARS levels were performed, for each sex, by case/control status. In the second set, we divided the study sample by diabetes status; TBARS levels were compared between diabetic and non-diabetic participants, within each sex for both cases and controls.

RESULTS

Cases were significantly older and less educated than controls in both sexes (mean age 55.1 ± 8.5 vs. 52.1 ± 9.5 years in women;
55.5 ± 9.0 vs. 52.4 ± 10.3 years in men). Among women, anthropometric measures were significantly higher in cases than in controls (mean BMI 31.2 ± 5.2 vs. 28.5 ± 6.8); likewise the prevalence of post-menopausal (76.4% vs. 56.9%) and non-white participants (19.4% vs. 8.1%) was significantly higher in cases than in controls. Cases of both sexes were significantly more likely to be current smokers, while there was a significantly larger prevalence of current drinkers in controls than in cases only among female participants. In both sexes, the prevalence of three major CHD risk factors such as type 2 diabetes, hypertension, and hypercholesterolemia was significantly higher in cases than in controls (diabetes 31.9% vs. 6.3% in women; 18.4% vs. 6.9% in men).

Triglycerides and fasting glucose were significantly correlated with TBARS levels in both women and men (correlation coefficients ranging from 0.21 for triglycerides to 0.51 for glucose). No significant correlations were found between TBARS and smoking, drinking or dietary variables.

In both sexes, after adjustment for potential confounders, there was no significant difference in TBARS levels between cases and controls [women: cases=1.38(nmol/ml) and control=1.34(nmol/ml); men: cases=1.37(nmol/ml) and controls=1.41(nmol/ml)].

However, in sub-group analyses by diabetes status (table 1) diabetic participants of both sexes, regardless of MI status, exhibited significantly higher TBARS values than non diabetic participants.

**CONCLUSIONS**

The present study adds to the growing literature on the strong association between lipid peroxidation and abnormalities in glucose and insulin metabolism (2-3, 7-8). Furthermore, our findings suggest that the observed associations of increased oxidative stress in individuals with clinical manifestations of atherosclerosis (such as MI) may be dependent on underlying abnormalities in glucose metabolism.

TBARS are strongly associated with glucose and triglycerides levels in the general population (2), and may be elevated in individuals with impaired glucose tolerance as well as in diabetics with poor metabolic control (3). The present study corroborates and extends these previous observations, indicating that, while type 2 diabetes may be an important correlate of lipid peroxidation, clinical CHD may not.

Among the limitations of this study, there is its observational nature and the fact that biomarkers of lipid peroxidation were measured after the occurrence of the clinical event. A further limitation is the limited specificity of TBARS as a marker of lipid peroxidation (9-10). Moreover, we relied on a self-reported history of medical diagnosis of type 2 diabetes and this may misrepresent the true prevalence of the disease. Finally, the participation rate is sub-optimal and may restrict the generalizability of the findings.

In summary, our findings suggest that the presence of lipid peroxidation in individuals with clinical manifestations of atherosclerosis may be dependent on underlying abnormalities in glucose metabolism, though it is not possible to rule out that, in the diabetic population, oxidative stress may have a significant role in the pathogenesis of CHD.

**ACKNOWLEDGMENTS**

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REFERENCES


Table 1. TBARS levels by diabetes status in controls and cases

<table>
<thead>
<tr>
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<th>Women</th>
<th></th>
<th>Men</th>
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<tbody>
<tr>
<td></td>
<td>Diabetic, n=22</td>
<td>Non-diabetic, n=47</td>
<td>Diabetic, n=33</td>
<td>Non-diabetic, n=146</td>
</tr>
<tr>
<td><strong>Unadjusted TBARS</strong></td>
<td><strong>1.81 (0.08)</strong> <strong>)</strong></td>
<td><strong>1.29 (0.06)</strong></td>
<td><strong>1.63 (0.07)</strong> <strong>)</strong></td>
<td><strong>1.35 (0.03)</strong></td>
</tr>
<tr>
<td><strong>Adjusted TBARS</strong></td>
<td><strong>1.84 (0.09)</strong> <strong>)</strong></td>
<td><strong>1.29 (0.06)</strong></td>
<td><strong>1.65 (0.08)</strong> <strong>)</strong></td>
<td><strong>1.36 (0.03)</strong></td>
</tr>
<tr>
<td></td>
<td>Diabetic, n=51</td>
<td>Non-diabetic, n=753</td>
<td>Diabetic, n=44</td>
<td>Non-diabetic, n=591</td>
</tr>
<tr>
<td><strong>Unadjusted TBARS</strong></td>
<td><strong>1.82 (0.05)</strong> <strong>)</strong></td>
<td><strong>1.31 (0.01)</strong></td>
<td><strong>1.97 (0.06)</strong> <strong>)</strong></td>
<td><strong>1.36 (0.02)</strong></td>
</tr>
<tr>
<td><strong>Adjusted TBARS</strong></td>
<td><strong>1.83 (0.06)</strong> <strong>)</strong></td>
<td><strong>1.31 (0.02)</strong></td>
<td><strong>1.97 (0.06)</strong> <strong>)</strong></td>
<td><strong>1.36 (0.02)</strong></td>
</tr>
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* Mean values (SE); multivariate model includes: age, education, race, BMI, physical activity, pack years of smoking, triglycerides, drinking status (past 12-24 months), and menopausal status (in women)

** $p \leq 0.001$