Oxidation, Type 2 Diabetes, and Coronary Heart Disease: A Complex Interaction

Findings from a population-based study

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OBJECTIVE — The purpose of this study was to analyze 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 New York: 257 women and men with incident MI and 1,452 healthy control subjects (aged 35–70 years). Lipid peroxidation was measured by plasma levels of thiobarbituric acid reactive substances (TBARS). History of type 2 diabetes was determined by self-reported history of medical diagnosis.

RESULTS — In multivariate analyses, there was no significant difference in TBARS levels between case and control subjects in both sexes. In subgroup analyses by diabetes status, diabetic subjects, regardless of MI status, exhibited significantly higher TBARS values than nondiabetic subjects. For diabetic women, TBARS values were 1.84 and 1.83 nmol/ml for case and control subjects, respectively. Values for nondiabetic women were 1.29 and 1.31 nmol/ml, respectively. In diabetic men, values were 1.65 and 1.97 nmol/ml for case and control subjects, respectively. Values for nondiabetic men were 1.36 and 1.36 nmol/ml, respectively.

CONCLUSIONS — Whereas type 2 diabetes may be an important correlate of lipid peroxidation, clinical coronary heart disease may not.

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Oxidation has been hypothesized to be one of the plausible pathogenic mechanisms underlying the associations between coronary heart disease (CHD) and abnormalities in glucose and insulin metabolism (1). Although 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 among 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 of 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 years and discharged alive with a diagnosis of acute incident MI (4) (ICD9 410) were recruited from hospitals in Erie and Niagara counties in New York State (75% of all 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 control subjects were interviewed, representing 59.5% of those identified, contacted, and for whom we could determine eligibility. Biomarkers of lipid peroxidation were available for 3,615 individuals (969 case and 2,646 control subjects) out of the total number of participants (n = 4,047; 1,197 case and 2,850 control subjects). The present study focuses on the 1,709 participants who were not taking statins or vitamins at the time of the interview (257 case and 1,452 control subjects). 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 measurements of resting blood pressure, 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 lifestyle habits, including dietary habits, alcohol consumption, and smoking history. The reference time frame for questions regarding dietary and alcohol consumption habits was 12–24 months before the MI (for case subjects) or the interview (for control subjects). Hypertension, type 2 diabetes, hypercholesterolemia, and smoking status were assessed at the time of the MI (for case subjects) or the time of interview (for control subjects).

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 before phlebotomy. The blood tubes used were immediately protected from light, kept at 4°C, processed, and stored at −80°C

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Table 1—*TBARS levels by diabetes status in control and case subjects*

	Women		Men	
	Diabetic	Nondiabetic	Diabetic	Nondiabetic
Case subjects				
n	22	47	33	146
Unadjusted TBARS	1.81 ± 0.08*	1.29 ± 0.06	1.63 ± 0.07*	1.35 ± 0.03
Adjusted TBARS	1.84 ± 0.09*	1.29 ± 0.06	1.65 ± 0.08*	1.36 ± 0.03
Control subjects				
n	51	753	44	591
Unadjusted TBARS	1.82 ± 0.05*	1.31 ± 0.01	1.97 ± 0.06*	1.36 ± 0.02
Adjusted TBARS	1.83 ± 0.06*	1.31 ± 0.02	1.97 ± 0.06*	1.36 ± 0.02

Data are means ± SE unless otherwise indicated. 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). *$P \leq 0.001$.

within 90 min 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 nondiabetic participants within each sex for both case and control subjects.

RESULTS — Case subjects were significantly older and less educated than control subjects in both sexes (mean ± SD 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 case than in control subjects (mean ± SD BMI 31.2 ± 5.2 vs. 28.5 ± 6.8 kg/m^2); likewise, the prevalence of postmenopausal (76.4 vs. 56.9%) and nonwhite participants (19.4 vs. 8.1%) was significantly higher in case than in control subjects. Case subjects of both sexes were significantly more likely to be current smokers, whereas there was a significantly larger prevalence of current drinkers in control subjects only among female participants. In both sexes, the prevalence of three major CHD risk factors (type 2 diabetes, hypertension, and hypercholesterolemia) was significantly higher in case than in control subjects (diagnosis of 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 case and control subjects (1.38 and 1.34 nmol/ml for case and control female subjects, respectively, and 1.37 and 1.41 nmol/ml for case and control male subjects, respectively).

However, in subgroup analyses by diabetes status (Table 1), diabetic participants of both sexes, regardless of MI status, exhibited significantly higher TBARS values than nondiabetic participants.

CONCLUSIONS — The present study adds to the growing body of 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 triglyceride levels in the general population (2) and may be elevated in individuals with impaired glucose tolerance and in diabetic subjects with poor metabolic control (3). The present study corroborates and extends these previous observations, indicating that, whereas type 2 diabetes may be an important correlate of lipid peroxidation, clinical CHD may not.

The limitations of this study include 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 suboptimal 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; however, it is not possible to rule out that, in the diabetic population, oxidative stress may have a significant role in the pathogenesis of CHD.

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