Predictors of Subclinical Atherosclerosis in Women With Spinal Cord Injury

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Background: Chronic spinal cord injury (SCI) is associated with an increase in risk factors for cardiovascular disease (CVD). In the general population, atherosclerosis in women occurs later than in men and usually presents differently. Associations between risk factors and incidence of CVD have not been studied in women with SCI.

Objective: To determine which risk factors for CVD are associated with increased carotid intima-media thickness (CIMT), a common indicator of atherosclerosis, in women with SCI.

Methods: One hundred and twenty-two females older than 18 years with traumatic SCI at least 2 years prior to entering the study were evaluated. Participants were asymptomatic and without evidence of CVD. Exclusion criteria were acute illness, overt heart disease, diabetes, and treatment with cardiac drugs, lipid-lowering medication, or antidiabetic agents. Measures for all participants were age, race, smoking status, level and completeness of injury, duration of injury, body mass index, serum lipids, fasting glucose, hemoglobin A1c, and ultrasonographic measurements of CIMT. Hierarchical multiple linear regression was conducted to predict CIMT from demographic and physiologic variables.

Results: Several variables were significantly correlated with CIMT during univariate analyses, including glucose, hemoglobin A1c, age, and race/ethnicity; but only age was significant in the hierarchical regression analysis. Conclusion: Our data indicate the importance of CVD in women with SCI.

Key words: age, cardiovascular disease, carotid intima-media thickness, hemoglobin A1c, risk factors, smoking

The secondary conditions of metabolic syndrome and cardiovascular disease (CVD) resulting from spinal cord injury (SCI) are not well understood. In particular, persons with SCI have an increase in metabolic risk factors for cardiovascular disease (CVD), but researchers have not determined whether this increase is associated with an increased incidence of CVD. The association has not been shown in reports on mortality or prevalence rates for CVD in people with SCI or in the few studies that have appraised CVD in people with SCI using physiologic assessments. Either the question was not addressed, or the evidence is insufficient due to low sample sizes and a lack of objective, prospective epidemiological studies assessing this question. Nevertheless, studies consistently show that metabolic syndrome is prevalent among individuals with SCI. Metabolic syndrome consists of multiple interrelated risk factors that increase the risk for atherosclerotic heart disease by 1.5- to 3-fold.

Compounding the uncertainty about the association of metabolic risk factors with CVD in SCI are possible gender differences. Findings from studies of men with SCI might not apply to women with SCI. For example, the correlation between physical activity and high-density lipoprotein (HDL) levels in men with SCI is not found for women with SCI. Furthermore, able-bodied women develop atherosclerosis later than do able-bodied men, and they usually present differently. Some studies indicate that abnormal glucose metabolism may play a particularly important role in CVD in women; data from our group suggest that this is the case in women with SCI as well. Although women constitute 18% to 20% of the SCI population, no studies have
evaluated cardiovascular health in women with chronic SCI.

Carotid intima-media thickness (CIMT) is the most robust, highly tested, and often used noninvasive endpoint for assessing the progression of subclinical atherosclerosis in men and women of all ages.28-46 For people with SCI, CIMT is a reliable surrogate measure of asymptomatic CVD.15,47 The incidence of asymptomatic CVD appears to increase with the duration of SCI,15 where duration of injury is a cardiac risk factor independent of age.17 Moreover, CIMT is greater in men with SCI than in matched able-bodied controls,48 indicating a subclinical and atypical presentation of CVD. A variety of studies have confirmed the usefulness of high-resolution B-mode ultrasound measurement of CIMT for quantitation of subclinical atherosclerosis.49

To better discern the association of risk factors with measures of subclinical atherosclerotic disease in women with SCI, we performed blood tests and ultrasonographic measurements of CIMT on 122 females with chronic SCI who were free of overt CVD. We tested for the 3 metabolic risk factors that are consistently identified in the varied definitions of metabolic syndrome: abnormal carbohydrate metabolism, abnormally high triglycerides, and abnormally low HDL cholesterol. We also tested for 4 other CVD risk factors: high levels of low-density lipoprotein (LDL), high total cholesterol, high body mass index (BMI), and a history of smoking.

Methods

Participants

Participants were recruited during 2001-2002 from a pool of women who had been evaluated at the local SCI clinic and through advertising on the clinic bulletin board and flyers in the community. Inclusion criteria were female sex, over the age of 18 years, traumatic SCI at least 2 years prior to entering the study, and asymptomatic without evidence of significant CVD. Exclusion criteria were acute illness, evidence of CVD such as history of myocardial infarction as indicated by positive history and electrocardiogram, congestive heart failure, coronary artery bypass surgery, stroke, unstable angina, diabetes, and treatment with cardiac drugs, lipid-lowering medication, or antidiabetic agents. The study was conducted in accordance with policies and procedures set forth by the local institutional review board.

Measures

Data collection

The study was conducted at the spinal cord injury medical home clinic, which is fully accessible to individuals with disabilities. Participants were asked to sign a consent form before any study procedures were performed. During the initial visit, a detailed history was taken and a physical examination was performed. Height, weight, and waist circumference measurements were obtained according to standard methodology. In addition, a 12-lead electrocardiogram (ECG) was performed in the supine position to evaluate the presence of silent abnormalities that indicate myocardial infarction or ischemia. A second visit was scheduled within 2 weeks of the initial visit. Participants were asked to fast and had laboratory blood tests drawn to measure total cholesterol, LDL and HDL fractions, triglycerides, fasting plasma glucose, and hemoglobin A1c. Hemoglobin A1c is a glycated form that serves as a standard marker of average blood glucose levels over the previous 1-3 months. A third visit took place within 2 weeks to review the laboratory findings and ECG results and to discuss the need for lifestyle intervention.

Carotid artery ultrasound image acquisition

High resolution B-mode carotid artery ultrasound images of the far wall of the carotid artery were obtained with a Hewlett-Packard L7540 7.5 MHz linear array transducer attached to an HP Sonos 5500 ultrasound imager according to the standardized procedures and technology of Hodis et al (patents 2005, 2006, 2011).28,49-51 Each ultrasound examination was duplicated, and images were electronically transmitted to the Core Imaging and Reading Center of the Atherosclerosis Research Unit, where the images underwent quality assurance and standardized image processing. As described previously, arterial
wall structures were measured by standardized methodology using automated computerized edge detection at subpixel resolution.\textsuperscript{30,31}

### Statistical analysis

Descriptive statistics were calculated for all variables (age, race, smoking status, level and completeness of injury, BMI, fasting glucose, hemoglobin A1c, total cholesterol, HDL, LDL, and triglycerides). After conducting univariate analyses, hierarchical multiple linear regression was conducted using IBM SPSS software (IBM, Armonk, NY) to predict CIMT, with the first block including demographic variables and the second block including physiologic variables. All variables were left in the model as covariates, regardless of significance. Categorical variables (race, smoking, injury type) were dummy coded into $k-1$ variables ($k =$ number of levels).

### Results

Characteristics of the 122 women in the study are presented in Table 1. Age and BMI were the only variables that were influenced by race. Hispanic women were significantly younger than their counterparts, $F(2, 114) = 4.79, P = .01$. Black women had a significantly higher BMI than their White counterparts, $F(2, 65) = 3.84, P = .03$. Preliminary analyses (Table 2) indicated several variables significantly related with CIMT including: glucose, hemoglobin A1c, and race/ethnicity.

The overall model was significant, $F(16, 46) = 8.53, P < .001$, and accounted for 66% of the variance. The adjusted $R^2$ (coefficient of multiple determination) was .54 for the first block of variables and increased significantly ($P = .006$) to .66 when the second block of variables was added. A significant predictor of CIMT at an alpha level of .05 was age ($R = .51$, $t = 4.79, P < .001$). Hemoglobin A1c approached significance ($R = .19$, $t = 1.99, P = .053$).

### Discussion

Our study shows that subclinical atherosclerosis, as measured by CIMT, in women with SCI is positively correlated with age. A1c was positively correlated with CIMT and just missed significance ($P = .053$); this shows promise for further investigation. If it can be verified with future research, this correlation with hemoglobin A1c, which reflects long-term glucose metabolism, would suggest that CIMT is associated with...
abnormal carbohydrate metabolism, and possibly metabolic syndrome, in women with SCI.

Consistent with our findings in this study, a related study by our group on a subset of this same female cohort found that CIMT was very highly correlated with hemoglobin A1c ($R = .93, P < .001$) and moderately correlated with blood glucose ($R = .22, P = .04$) (mean age, 42 ± 11 years; injury duration 16 ± 10 years; White 29%, Black 23%, Hispanic 43%, other race/ethnicity 5%; complete paraplegia 40%, incomplete paraplegia 25%, complete tetraplegia 18%, incomplete tetraplegia 17%). The strength of the correlation between hemoglobin A1c and CIMT that was found in that smaller sample of 65 women supports our premise that this correlation represents a clinically important effect. Furthermore, the significant correlation of blood glucose with CIMT in the subset study also implicates abnormal carbohydrate metabolism. The subset study found a correlation of CIMT with duration of injury independent of age. Duration of injury is a predictor of subclinical CVD in individuals with SCI who have abnormal lipid profiles.

This study shows no significant correlation of CIMT with lipid profile, BMI, or race when using regression analyses. These findings are supported by other recent studies. Lipid profiles have been shown to stabilize within 5 years after inpatient SCI rehabilitation. BMI underestimates adiposity in this population, because women who use wheelchairs have greater lean mass in their upper extremities than do able-bodied controls. Total body fat mass is greater in women with paraplegia; for the equivalent total body-fat mass, BMI is lower in women with paraplegia. Race/ethnicity as a predictor was confounded by the mean age of the large Hispanic group, which was substantially younger. One reason for this demographic difference may be that race/ethnicity is associated with disparities influenced by poverty. Low income (an indicator of poor access to services) is clearly linked to early mortality after SCI, and those with better outcomes are more likely to survive. Therefore, restricted access to health care may have played a selective role, increasing mortality in the Hispanic group.

Limitations

Perhaps the largest limitation of the present study was use of a convenience sample. Participants were either outpatients at the local spinal cord injury clinic or were outpatient volunteers responding to advertising on the clinic bulletin board and community advertising. Therefore the results may not apply to women with SCI who are more reluctant to participate or who are isolated from the community; it is possible that the more isolated women would present with different cardiovascular health profiles compared to those participating in the study. A second limitation is the localized geographic region. Participants were living in Southern California and may have different cardiovascular health profiles compared to women with SCI in other regions.

Conclusions

The significance of emerging cardiovascular risk factors in women with SCI warrants further attention. Given that CIMT is reported to be increased in younger asymptomatic men with SCI compared to able-bodied matched controls (mean age, 32; duration, 7 years), we suggest that accelerated atherosclerosis in older asymptomatic women with SCI (mean age, 43; duration, 16 years) constitutes a clinically important condition. Our previously reported long-term longitudinal study supports this conclusion.

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