ORIGINAL ARTICLE

Elevated C-Reactive Protein Associated With Decreased High-Density Lipoprotein Cholesterol in Men With Spinal Cord Injury

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ABSTRACT. Liang H, Mojtahedi MC, Chen D, Braunschweig CL. Elevated C-reactive protein associated with decreased high-density lipoprotein cholesterol in men with spinal cord injury. Arch Phys Med Rehabil 2008;89:36-41.

Objectives: To determine if people with spinal cord injury (SCI) have elevated C-reactive protein (CRP), to examine the association of CRP with high-density lipoprotein cholesterol (HDL-C), and to assess the influence of completeness and level of injury on these parameters.

Design: Cross-sectional.

Setting: Urban university.

Participants: Men with SCI (n=129) who were free of infection and/or recent anti-inflammatory medication use as well as their 1:1 age- and race-matched able-bodied counterparts from the 1999–2002 National Health and Nutrition Examination Surveys.

Interventions: Not applicable.

Main Outcome Measures: High CRP was defined as 3mg/L or higher and low HDL-C as less than 1.04mmol/L.

Results: Men with SCI were more likely to have high CRP (odds ratio [OR]=2.29; 95% confidence interval [CI], 1.33–3.95) and low HDL-C (OR=1.81; 95% CI, 1.01–3.27). The OR for low HDL-C in SCI was no longer significant when high CRP was controlled. CRP was higher in complete versus incomplete injury (median, 3.7mg/L vs 1.2mg/L; $P=.005$), and this elevation was independent of age, smoking, physical activity, waist circumference, and weight. No conclusion can be made on the association of injury level and CRP because of a lack of power.

Conclusions: The elevated CRP, possibly the major risk factor, together with decreased HDL-C may contribute to greater incidence for cardiovascular disease in the SCI population.

Key Words: C-reactive protein; Cholesterol, HDL; Cross-sectional studies; Rehabilitation; Risk factors; Spinal cord injuries.

MORBIDITY AND MORTALITY from cardiovascular disease (CVD) is greater among spinal cord–injured compared with able-bodied populations.[1-4] It was recently found that adult men with a spinal cord injury (SCI) had better metabolic profiles for all traditional risk factors for CVD, except high-density lipoprotein cholesterol (HDL-C), than their age- and race-matched able-bodied counterparts.[5] These findings suggest that nontraditional risk factors may at least partially explain their increased disease rates. C-reactive protein (CRP), a nontraditional risk factor, is a marker of inflammation that has been shown to predict CVD across populations.[6-10] The American Heart Association recommends the measurement of CRP for CVD risk in certain populations.[11] Few studies have examined CRP concentrations in SCI populations, and these have not included appropriate comparison groups and/or did not control for other known influences on CRP (eg, waist, race, age, smoking).[12-14]

HDL-C has antioxidant[15] and anti-inflammatory[16] functions; however, in conditions of chronic inflammation, these functions become defective.[17,18] In patients with severe inflammation, such as rheumatoid arthritis, lower HDL-C has been associated with higher CRP and subclinical atherosclerosis.[19] Among SCI populations, lower HDL-C has been well established for over 2 decades[20,21]; however, the relationship between HDL-C and CRP in this population is unknown.

People with tetraplegia tend to have lower HDL-C than those with paraplegia; however, the completeness of injury does not impact HDL-C levels.[22] Whether the completeness or level of injury is associated with different CRP concentrations has not been examined. The purpose of this study was to examine whether people with SCI have elevated CRP compared with the able-bodied population and to assess the association of CRP with HDL-C and the influence of completeness and level of injury on these parameters. Our study will provide new insights into assessing CVD risk by using traditional and nontraditional markers as well as disability-related risk factors. Understanding these parameters in SCI populations will assist in the development of more effective prevention strategies tailored to specifically target those with great CVD risk.

METHODS

A cross-sectional study design was used to investigate differences in inflammation and HDL-C status between SCI and able-bodied men matched for race and age. This matching criterion was used to control for variables that are known to influence the primary outcomes of interest including HDL-C and CRP.[23,24]

Participants

Men with SCI. Men with SCI were recruited by using flyers and word of mouth from clinic waiting areas at the Rehabilitation Institute of Chicago at Northwestern University. Eligibility criteria for participation included being between 20 and 59 years old, at least 1 year post-SCI, and free of acute inflammatory diseases or infections (eg, urinary tract infection

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[UTI], pressure ulcer) or current medication use for these infections.[25] At the time of recruitment, questions including "Do you currently have pressure sores or skin ulcers?" and "Do you currently have a urinary tract infection?" were used for screening. Persons who answered "yes" to either question or took medications for treating infections were excluded. Those who were reported to have a history of diabetes, hypertension, or high cholesterol were not excluded.

Able-bodied men. A dataset of able-bodied men was created from the 1999–2002 National Health and Nutrition Examination Surveys (NHANES)[26] by using 1:1 matching on age and race with SCI participants.

Eligibility and Subject Matching

Eligibility criteria for the able-bodied included men without paralysis or amputation and having complete data on age, weight, waist circumference, HDL-C, CRP, and information on disease history and smoking status. Information on acute inflammatory diseases or infections was not available in NHANES. Therefore, no exclusion regarding infections was made. Matching was based on age (within 5y), sex, and race. The record having the same race and sex and minimum age difference with the SCI participant was selected as a control. To guarantee no duplication of controls, an able-bodied record was deleted after being selected from the NHANES dataset and no longer available for further matching. The dataset with able-bodied controls was vertically merged with the SCI dataset before analysis. This research was approved by the institutional review boards of Northwestern University and the University of Illinois at Chicago.

Study Variables

Demographic characteristics consisted of age, race, smoking status (yes, no), diabetes, hypertension, and high cholesterol history. The SCI men were also assessed for age at injury, time since injury, injury level, and completeness of injury. This injury-related information was mostly self-reported; when participants could not remember, their medical records were obtained for such information. The neurologic injury level was defined as the first spinal vertebral level (ie, C2-8, T1-12, L1-5, S1-5) that shows abnormal neurologic loss. For example, if a participant's injury level was T11-12, his injury level was defined as T11. Because the sympathetic nervous system modulates the immune responses by inhibiting the production of proinflammatory cytokines and stimulates the production of anti-inflammatory cytokines[27,28] and a high level of SCI (injury at or above spinal cord T6) reduces sympathetic input, the injury level was classified as an injury site at or above T6 (yes, no). Complete injury was defined as no motor or sensory function in the anal and perineal region representing the lowest sacral (S4-5) cord; incomplete injury was defined as otherwise.[29]

Anthropometric measures included weight and waist circumference. Men with SCI were weighed in their wheelchair by using a wheelchair scale,[a] calibrated for accuracy daily to within 0.1kg, and then transferred out of their wheelchairs while their wheelchairs were weighed. The able-bodied men were weighed on a beam scale by using standardized methodologies used during NHANES data collection. Both SCI and able-bodied men wore minimal clothing when weights were obtained. The waist circumference measurement technique differed between the groups. The supine waist was obtained for the SCI men because standing waist circumference is not feasible.[30] The men in NHANES had their waist circumference assessed while standing. Recumbent and standing measures of waist circumference are highly comparable.[31] Both groups had 3 measurements taken at the high point of the iliac crest to the nearest 0.1cm with minimal expiration, and the average was used for data analysis.

All participants had blood samples obtained after a minimum of 9 hours of fasting. For SCI subjects, a reminder call at least 24 hours before their blood-draw appointment was made, and screening questions were repeated to make sure they were clear of infections for blood draw. If the participants answered "yes" to pressure ulcer or UTI when the reminder call was made, their blood-draw appointment was cancelled, and they were asked to reschedule with the researcher 1 week after finishing their antibiotic medication. The analysis of serum CRP and HDL-C in NHANES 1999–2002 has previously been described.[32,33] The measurement of CRP in SCI was conducted by Medical Research Laboratories International. High-sensitivity CRP concentrations in both NHANES and in blood samples from SCI men were measured by using latex-enhanced nephelometry.[32] A cholesterol oxidase assay was used to measure serum HDL-C in SCI and able-bodied men.

The physical activity level in SCI men was assessed by the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD).[34] This is a validated questionnaire with 13 items designed for people with physical disabilities, which asks the number of days and hours a day in the past 7 days subjects participated in recreational, household, and occupational activities. The total physical activity metabolic equivalents (METS) score for the PASIPD was created by multiplying the average hours per day for each activity by an METS value associated with the intensity of the activity and summing over activities 2 through 13.[35] By using this scoring procedure, the mathematically maximum possible score is 199.5 METS per day.

Data Analysis

The means and interquartile ranges (IQRs) were used for all continuous variables for consistency because outcome variables CRP and HDL-C were nonnormally distributed. Frequencies were used as descriptors for dichotomous variables including complete injury (yes, no); injury level at or above T6 (yes, no); current smoking (yes, no); and disease history (yes, no) of diabetes, hypertension, and high cholesterol. For differences between SCI and the able-bodied, a dependent *t* test and Wilcoxon signed-rank test were conducted for paired continuous variables, and the McNemar test was used for dichotomous variables. To eliminate the effect of disease history on CRP and HDL-C, we performed the Wilcoxon rank-sum test because an unequal sample size occurred in SCI and able-bodied patients when we excluded those who had a history for diabetes, hypertension, or high cholesterol. Conditional logistic regression was used to examine the odds ratios (ORs) and 95% confidence intervals (CIs) for having high CRP and low HDL-C in SCI versus able-bodied men while controlling for smoking and waist circumference. High CRP was defined as a CRP level of 3mg/L or higher[36] and low HDL-C as an HDL-C level of less than 1.04mmol/L.[37] For comparisons of complete versus incomplete and high (T6 and above) versus low (below T6) injury within SCI men, the Wilcoxon rank-sum test was performed to test differences for continuous variables and the chi-square test was used for dichotomous variables. Post hoc power analysis, which used the sample size and effect size in the study, was conducted based on the comparisons of 2 sample means difference for log CRP between SCI and the able-bodied and between complete versus incomplete and high versus low injury within SCI.

To examine the association between CRP and HDL-C in SCI and able-bodied subjects, the Spearman rank correlation was