

ORIGINAL ARTICLE

C-Reactive protein in adults with chronic spinal cord injury: increased chronic inflammation in tetraplegia vs paraplegia

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Study design: Cross-sectional.

Objectives: In community-dwelling adults with chronic spinal cord injury (SCI), to (1) quantify C-reactive protein (CRP), a marker of inflammation and cardiovascular disease (CVD) risk; (2) determine factors associated with CRP.

Setting: Hamilton, Ontario, Canada.

Methods: We examined CVD risk factors in 69 participants. Measurements included length, weight, waist circumference, blood pressure, percent fat mass (bioelectrical impedance analysis) and fasting blood parameters (high-sensitivity CRP, lipids, insulin, glucose, insulin resistance by homeostasis model assessment (HOMA)).

Results: Mean CRP of the group was $3.37 \pm 2.86 \text{ mg l}^{-1}$, consistent with the American Heart Association (AHA) definition of high risk of CVD. CRP was 74% higher in persons with tetraplegia (4.31 ± 2.97) than those with paraplegia ($2.47 \pm 2.47 \text{ mg l}^{-1}$, $P = 0.002$), consistent with high CVD risk. Participants with high CRP ($3.1\text{--}9.9 \text{ mg l}^{-1}$) had greater waist circumference, BMI, percent fat mass and HOMA values than those with lower CRP ($\leq 3.0 \text{ mg l}^{-1}$, all $P < 0.05$). LogCRP was independently correlated with waist circumference ($r = 0.612$), logTriglycerides ($r = 0.342$), logInsulin ($r = 0.309$) and logHOMA ($r = 0.316$, all $P < 0.05$). Only level of lesion and waist circumference remained significantly associated with logCRP when variables with significant bivariate correlations were included in multiple regression analysis.

Conclusion: Mean CRP values in this sample of adults with chronic SCI were consistent with the AHA classification of high CVD risk, especially those of persons with tetraplegia. Level of lesion and waist circumference are independently associated with CRP in this population.

Spinal Cord advance online publication, 15 April 2008; doi:10.1038/sc.2008.32

Keywords: C-reactive protein; spinal cord injury; cardiovascular disease; inflammation; SHAPE-SCI

Introduction

Management of acute spinal cord injury (SCI) has improved dramatically in recent years. Mortality in the first 2 years

post injury has decreased by 40% in the past three decades.¹ However, a longer life also confers greater risk for development of chronic diseases. Diabetes is particularly prevalent in the chronic SCI population, with some studies reporting up to 20% prevalence,² as compared with 8.8% in the able-bodied population.³ Also, similar to the able-bodied population,⁴ cardiovascular disease (CVD) is the leading cause of death after long-term SCI.⁵

Compared with able-bodied persons, those with SCI are at increased risk for CVD. Higher low-density lipoprotein cholesterol (LDL), lower high-density lipoprotein cholesterol (HDL) and an 8–18% greater fat mass have been reported in chronic SCI than in able-bodied participants.^{6,7} Level and completeness of spinal cord lesion contribute to risk for CVD;⁸ those with tetraplegia are at 16% greater risk of CVD than those with paraplegia, and more complete lesions are associated with an excess 44% CVD risk.

It is increasingly accepted that diseases associated with CVD, such as atherosclerosis, are inflammatory in nature.⁹ A commonly used measure of inflammation, particularly at subclinical levels, is C-reactive protein (CRP). CRP is secreted

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Received 3 September 2007; revised 6 December 2007; accepted 27 February 2008

by the liver during the acute phase of inflammation. Recent large, epidemiological studies in able-bodied populations have shown that elevated CRP levels are predictive of cardiovascular events.^{10,11} CRP is an independent risk factor for CVD, providing similar predictive power as the metabolic syndrome, a well established constellation of cardiovascular risk factors.¹⁰ The American Heart Association (AHA) has set clinical guidelines for CRP, with values of >3.0 , 1.0 – 3.0 and <1.0 mg l^{-1} corresponding to high, average and low CVD risk.¹²

Preliminary evidence suggests a state of chronic inflammation in the SCI population. Manns *et al.*¹³ reported a mean CRP level of 3.0 mg l^{-1} in 22 men with paraplegia, considered borderline high CVD risk using the AHA classification system. In a group of 93 men and women with SCI, Lee *et al.*¹⁴ found that CRP was elevated ($P < 0.05$) among individuals with a high (≥ 6) Framingham risk score (a widely used clinical tool for predicting CVD), and in those with dyslipidemia and insulin resistance, however actual CRP values were not reported. In another study, Frost *et al.*¹⁵ demonstrated that mean CRP was 274% higher ($P = 0.001$) in 37 men with SCI than in 10 able-bodied controls. Despite these preliminary findings, no study has reported factors associated with CRP values.

The objectives of our study were to quantify, and determine factors associated with, CRP, in a large community-dwelling sample of adults with chronic SCI.

Materials and methods

Participants

Data were obtained from the multicenter Study of Health and Activity in People with Spinal Cord Injury (SHAPE-SCI) in Ontario, Canada, for which complete methods have been published.¹⁶ The data presented herein are part of the SHAPE-SCI Risk Factor substudy. A total of 75 apparently healthy community-dwelling adults with chronic SCI were recruited from Hamilton, Ontario. Of these, CRP values were unavailable for 6 participants with tetraplegia, therefore data are reported on a total of 69 participants ($n = 56$ males; $n = 13$ females). There were no differences in any other study variables between participants for whom CRP values were available and those for whom these were not available (data not shown). Level of spinal cord lesion was classified as either paraplegia ($n = 37$) or tetraplegia ($n = 32$). Self-reported completeness of lesion was defined as either complete ($n = 26$) or incomplete ($n = 42$). Completeness of lesion was unknown for one participant.

Protocols for SHAPE-SCI and the Risk Factor substudy were approved by the University of Guelph and McMaster University Research Ethics Boards. Participants provided written informed consent prior to enrollment and were given a nominal honorarium for participating.

Measurements

All data were collected in the participants' homes, by two trained research assistants, after a minimum 12 h fast. Blood pressure was measured in the right arm, in the seated

position after a 5 min rest, using a stethoscope and sphygmomanometer. Participants were weighed to the nearest 0.1 kg in light clothing with shoes removed using a portable, digital, wheelchair scale (Health O Meter 2450KL, Brooklyn, NY, USA). The scale was calibrated at each visit with two 15 lb weights. Weight of wheelchair-plus-participant was measured, followed by weight of wheelchair alone. Body weight was determined by subtracting wheelchair weight from wheelchair-plus-participant weight. Participants then transferred to a spine board (National Lifesaving Society item EQ-10, Edmonton, Alberta, Canada) placed on a bed. Waist circumference (WC) was measured to the nearest 0.1 cm at the lowest rib, after exhalation, with participants lying supine on the spine board with arms abducted 30° from the midline. Supine length (stature) was measured to the nearest 0.1 cm with participants lying on the spine board, using a flexible tape measure extended from heel to crown. For participants with contractures, length was defined as the sum of segmental lengths (heel to knee, knee to hip, hip to crown). Body composition was also determined with participants lying supine using bioelectrical impedance analysis (RJL Systems Bioelectrical Body Composition Analyzer Quantum II, Clinton Township, MI, USA), and percent fat mass (%FM) was calculated using NHANES III reference data.¹⁷

Venous blood was collected into vacutainer tubes with anticoagulant for glucose, kept on ice and shielded from light until analyzed by the Department of Laboratory Medicine at McMaster Medical Centre. The blood was then centrifuged at 3000 rpm and analyzed the same day. Some insulin samples were not analyzed on the day of collection; these were frozen at -80°C until analysis. Lipid concentrations (total cholesterol (TC) and triglycerides (TG)) were measured using an enzymatic colorimetric assay. HDL-cholesterol was measured using a homogeneous enzymatic colorimetric assay, and LDL-cholesterol values were determined using the Friedewald equation.¹⁸ Fasting glucose was measured using the hexokinase method. All above tests were performed on an automated machine (Roche Modular ISE 1800, Roche, Laval, Québec, Canada). Fasting insulin was determined using a chemiluminescent immunometric assay (IMMULITE 2000, Intermedico, Holliston, MA, USA). Insulin and glucose values were used to determine insulin sensitivity, using the homeostasis model assessment (HOMA).¹⁹ High-sensitivity CRP was determined via particle enhanced immunonephelometry (CardioPhase hsCRP, Dade Behring; Mississauga, Ontario, Canada), allowing for detection of CRP at concentrations lower than those found in systemic inflammation.

Data analysis

Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS Version 14.0, Chicago, IL, USA); unless otherwise noted, $P \leq 0.05$ was considered statistically significant. All variables were normally distributed and are presented as mean \pm s.d., with the exception of CRP, glucose, insulin, HOMA, TC:HDL ratio, and TG levels which were log transformed for analysis. CRP was

not significantly different between participants with self-reported infection ($n=8$), or those receiving statin therapy ($n=7$, data not shown); these participants were therefore included in analyses. Participants with CRP levels $\geq 10 \text{ mg l}^{-1}$ ($n=12$), indicative of an acute phase response to inflammation,¹² were excluded from analysis where noted to ensure that CRP values used were indicative of low-grade inflammation. The frequency of infection was not different between those excluded due to CRP $\geq 10 \text{ mg l}^{-1}$, and those not excluded (data not shown). Participants were then categorized as having lower ($\leq 3.0 \text{ mg l}^{-1}$) or high ($3.1\text{--}9.9 \text{ mg l}^{-1}$) CRP values and between-group comparisons were made using *t*-tests. Significant findings for non-normally distributed variables were confirmed using non-parametric methods (Mann–Whitney's *U*-test, data not shown). *P*-values for multiple comparisons were adjusted using the Bonferroni method. Bivariate correlations were calculated between logCRP and selected variables. Those variables found to have significant bivariate correlations with logCRP were analyzed using forward linear regression modeling to determine which variables remained significantly and independently associated with CRP when considered together with other variables. Entry was allowed when the F-score probability was ≤ 0.05 .

We certify that all applicable institutional and governmental regulations concerning the ethical use of

human volunteers were followed during the course of this research.

Results

Background characteristics of participants (whole group and by level of lesion) are presented in Table 1 and biochemical parameters in Table 2. Level of lesion was evenly distributed between paraplegia (54%) and tetraplegia (46%). Thirty-eight percent of participants had complete spinal cord lesions compared to 62% with incomplete lesions. The average age of participants was 42.4 ± 12.0 years, and participants had been injured for a mean of 14.7 ± 10.4 years. Mean BMI was $25.8 \pm 5.1 \text{ kg m}^{-2}$, indicating that overall, the sample population was overweight. Percent FM was greater in tetraplegia than paraplegia ($P=0.021$). Other physical characteristics were not different. Comparisons between men and women yielded no significant results (data not shown).

All biochemical parameters, with the exception of HDL-cholesterol and CRP, fell within normal ranges, and were not different between participants with tetraplegia and paraplegia. Mean HDL-cholesterol was low ($1.21 \pm 0.33 \text{ mmol l}^{-1}$). After elimination of participants with CRP values $\geq 10 \text{ mg l}^{-1}$ ($n=12$), ensuring that CRP values represented low-grade inflammation, mean CRP of the whole group was high ($3.37 \pm 2.86 \text{ mg l}^{-1}$). Further, CRP was 74%

Table 1 Background characteristics of participants ($n=69$, unless otherwise indicated)

| | Mean \pm s.d. | | | Range |
|----------------------------|-----------------|-----------------------|------------------------|-------------|
| | Total sample | Paraplegia ($n=37$) | Tetraplegia ($n=32$) | |
| Age | 42.4 ± 12.0 | 41.2 ± 10.9 | 43.8 ± 13.2 | 21–79 |
| Years post injury | 14.7 ± 10.4 | 13.0 ± 10.1 | 16.8 ± 10.5 | 1–47 |
| Weight (kg) | 78.4 ± 15.8 | 76.9 ± 14.5 | 80.2 ± 17.5 | 47.3–134.5 |
| Length (cm) | 174.3 ± 8.9 | 173.7 ± 9.1 | 175.1 ± 8.8 | 147.6–197.2 |
| BMI (kg m^{-2}) | 25.8 ± 5.1 | 25.5 ± 4.8 | 26.2 ± 5.6 | 17.2–40.9 |
| Waist circumference (cm) | 91.7 ± 14.3 | 90.0 ± 14.2 | 93.5 ± 14.5 | 64.5–134.5 |
| Fat mass (%) ($n=47$) | 39.2 ± 10.0 | 36.6 ± 9.9 | 42.4 ± 9.4^a | 16.1–62.5 |

^a $P=0.021$; all other comparisons not significant.

Table 2 Fasting biochemical characteristics of participants ($n=69$, unless otherwise indicated)

| | Mean \pm s.d. | | | Range |
|---|-----------------|-----------------------|------------------------|------------|
| | Whole group | Paraplegia ($n=37$) | Tetraplegia ($n=32$) | |
| Cholesterol ^a (mmol l^{-1}) | 4.63 ± 1.06 | 4.77 ± 1.14 | 4.48 ± 0.95 | 2.89–7.13 |
| LDL ^a (mmol l^{-1}) | 2.75 ± 0.99 | 2.86 ± 1.01 | 2.61 ± 0.96 | 0.85–5.55 |
| HDL ^a (mmol l^{-1}) | 1.21 ± 0.33 | 1.24 ± 0.27 | 1.18 ± 0.38 | 0.4–2.6 |
| TC:HDL ratio ^a | 4.08 ± 1.43 | 4.03 ± 1.33 | 4.13 ± 1.54 | 1.66–8.66 |
| Triglycerides ^a (mmol l^{-1}) | 1.47 ± 0.86 | 1.46 ± 0.90 | 1.49 ± 0.82 | 0.44–4.82 |
| Glucose (mmol l^{-1}) | 5.21 ± 1.00 | 5.15 ± 1.04 | 5.28 ± 0.95 | 4.0–10.2 |
| Insulin ^a (pmol l^{-1}) | 67.5 ± 63.0 | 58.4 ± 57.7 | 78.1 ± 68.1 | 13.0–283.0 |
| HOMA ^a | 2.23 ± 2.11 | 1.88 ± 1.79 | 2.64 ± 2.40 | 0.4–8.1 |
| CRP (mg l^{-1}) | 8.60 ± 18.8 | 11.0 ± 25.1 | 5.77 ± 5.33 | 0.1–110.0 |
| CRP ^b (mg l^{-1}) ($n=57$) | 3.37 ± 2.86 | 2.47 ± 2.47 | 4.31 ± 2.97^c | 0.1–9.3 |

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; LDL, low density lipoprotein cholesterol; TC, total cholesterol.

^a $n=66\text{--}68$ for these variables.

^b $n=57$ participants with CRP $< 10 \text{ mg l}^{-1}$.

^c $P=0.002$.

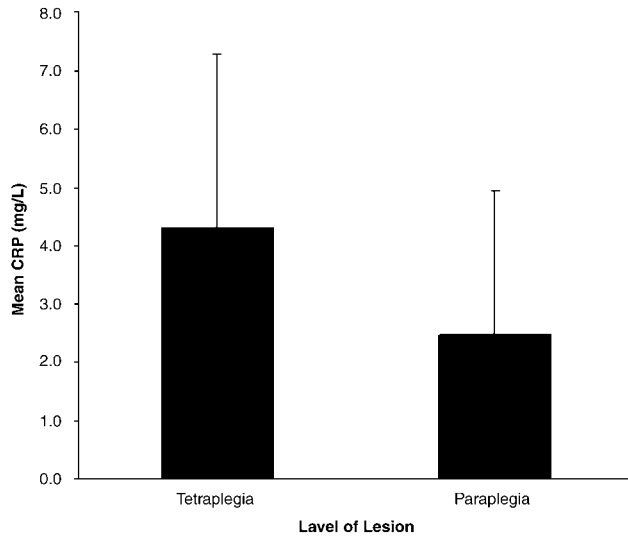


Figure 1 Mean \pm s.d. of C-reactive protein (CRP) levels between adults with tetraplegia (4.31 ± 2.97 , $n=28$) vs paraplegia (2.47 ± 2.47 mg l^{-1} , $n=29$), $P=0.002$.

Table 3 Differences between participants with lower (≤ 3.0 mg l^{-1}) vs high (3.1 – 9.9 mg l^{-1}) CRP values

| | Lower CRP ($n=33$) | High CRP ($n=24$) | P |
|--|-------------------------|------------------------|---------------------|
| Years post injury | 11.2 ± 8.1 | 19.8 ± 11.6 | 0.003 ^a |
| Waist circumference (cm) | 85.5 ± 13.9 | 97.6 ± 9.30 | <0.001 ^a |
| BMI ^b (kg m^{-2}) | 23.9 ± 4.29 | 26.0 ± 4.15 | 0.010 |
| Fat mass ^{b,c} (%) | 35.4 ± 9.37 | 43.6 ± 9.96 | 0.004 ^a |
| Cholesterol (mmol l^{-1}) | 4.60 ± 1.13 | 4.64 ± 1.12 | 0.902 |
| HDL-cholesterol (mmol l^{-1}) | 1.30 ± 0.37 | 1.11 ± 0.26 | 0.024 |
| LDL-cholesterol ^{b,c} (mmol l^{-1}) | 2.70 ± 1.01 | 2.73 ± 1.13 | 0.897 |
| TC:HDL ratio ^c | 3.79 ± 1.42 | 4.44 ± 1.58 | 0.073 |
| Triglycerides (mmol l^{-1}) | 1.12 ± 0.15 | 1.57 ± 0.19 | 0.019 |
| Glucose (mmol l^{-1}) | 5.00 ± 0.73 | 5.54 ± 1.37 | 0.071 |
| Insulin (pmol l^{-1}) | 49.8 ± 51.6 | 94.4 ± 74.0 | 0.006 |
| HOMA | 1.56 ± 1.48 | 3.27 ± 2.58 | 0.004 ^a |

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; LDL, low density lipoprotein cholesterol; TC, total cholesterol.

^aBonferroni corrected P -value = 0.004.

^b $n=29$ – 32 for lower CRP group.

^c $n=22$ – 23 for high CRP group.

higher in persons with tetraplegia (4.31 ± 2.97) than those with paraplegia (2.47 ± 2.47 mg l^{-1} , $P=0.002$; Figure 1). Mean CRP was not different between those with complete (3.18 ± 2.75) and incomplete injuries (3.50 ± 2.86 mg l^{-1} , $P=0.671$). Biochemical characteristics were not different between men and women (data not shown).

Differences in clinical parameters between participants with high (3.1 – 9.9 mg l^{-1}) and lower (≤ 3.0 mg l^{-1}) CRP are outlined in Table 3. The high CRP group had been injured longer (19.8 ± 11.6 vs 11.2 ± 8.1 y, $P<0.001$), and had greater WC (97.6 ± 9.30 vs 85.5 ± 13.9 cm, $P<0.001$), %FM (43.6 ± 9.96 vs $35.4 \pm 9.37\%$, $P=0.004$) and HOMA scores (3.27 ± 2.58 vs 1.56 ± 1.48 , $P=0.004$) than the lower CRP group.

Table 4 Correlation coefficients between logCRP and continuous study variables

| | r | P |
|--|--------|--------|
| Age (years) | 0.259 | 0.052 |
| Years post injury | 0.256 | 0.055 |
| Level of lesion | 0.396 | 0.002 |
| Waist circumference (cm) | 0.612 | <0.001 |
| BMI (kg m^{-2}) | 0.473 | <0.001 |
| Fat mass (%) | 0.365 | 0.008 |
| HDL-cholesterol (mmol l^{-1}) | -0.295 | 0.026 |
| LDL-cholesterol (mmol l^{-1}) | 0.088 | 0.525 |
| TC:HDL ratio | 0.261 | 0.050 |
| LogTriglycerides | 0.342 | 0.009 |
| LogGlucose | 0.157 | 0.245 |
| Loginsulin | 0.309 | 0.019 |
| LogHOMA | 0.316 | 0.016 |

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; LDL, low density lipoprotein cholesterol; TC, total cholesterol.

LogCRP was independently correlated with WC ($r=0.612$, $P<0.001$), BMI ($r=0.473$, $P<0.001$), %FM ($r=0.356$, $P=0.008$), logHOMA ($r=0.316$, $P=0.016$), logTG ($r=0.342$, $P=0.009$), logTC:HDL ($r=0.261$, $P=0.050$) and logInsulin ($r=0.309$, $P=0.019$; Table 4). These variables were added to a forward multiple regression model. Only level of lesion ($\beta=0.311$, $P=0.005$) and WC ($\beta=0.578$, $P<0.001$) remained significantly and independently associated with logCRP levels. Together, these variables explained 46.7% of the variance in logCRP.

Discussion

The main findings of this study of a representative²⁰ sample population of adults with chronic spinal cord injury were (1) mean CRP values of the group as a whole were consistent with the AHA definition of high CVD risk; (2) individuals with tetraplegia had 74% higher CRP values than those with paraplegia; (3) level of lesion and WC are significantly and independently associated with CRP in this population.

The mean CRP value for the entire study population suggests that individuals with chronic SCI, particularly those with tetraplegia, have high levels of low-grade inflammation. Our finding of higher CRP values in persons with tetraplegia vs those with paraplegia is in contrast to previous reports, where no significant relationships between CRP and level of lesion were found.^{14,15} However, the inconsistency may be due to differences between study populations. Lee *et al.*¹⁴ included only 40% of participants with paraplegia, compared to 54% in our study. In the study of Frost *et al.*,¹⁵ the sample size was 37, and so may have lacked the statistical power needed to detect a difference between persons with paraplegia and tetraplegia.

We also found individuals with tetraplegia to have higher %FM than those with paraplegia. Taken together, our findings are in agreement with the previously reported elevated CVD risk in tetraplegia.⁸ We found no significant differences in other CVD risk parameters between tetraplegia and paraplegia, nor did we find any significant differences between participants with complete and incomplete lesions.

Level of lesion had a stronger association with CVD risk in our study than completeness of lesion. We lacked a sufficient sample size to stratify lesions based on ASIA classification.

Participants with high CRP levels demonstrated an increased risk profile for CVD than those with lower CRP levels. Individuals with high CRP had higher adiposity as measured by %FM and WC. The relationship between measures of adiposity and CRP has been previously described.²¹ HOMA values were also higher in the high CRP group, indicative of greater insulin resistance, a condition shown to precede type II diabetes and to be an independent risk factor for CVD.²²

Our study aimed to examine factors related to CRP. We found that logCRP was highly correlated with indices of adiposity (WC, BMI, %FM). LogCRP was weakly correlated with only TC:HDL ratio, but with no other lipid marker classically used in determining CVD risk (that is, TC, TG and HDL- and LDL cholesterol). Apart from lower HDL which has been described previously in this population,⁶ lipid values fell within normal ranges. Thus, the CRP levels of this group were elevated independent of dyslipidemia, consistent with CRP being considered an independent CVD risk factor. These findings suggest that the markers of CVD risk typically used in the able-bodied population may not identify at-risk individuals with SCI. This is explored more fully in our second article in this issue of *Spinal Cord* (Finnie, Buchholz, Martin Ginis, SHAPE SCI Research Group; advance online publication 11 March 2008; doi:10.1038/sc.2008.21).

The only factors significantly and independently associated with CRP in this study were level of lesion and WC. WC is widely used as a measure of abdominal obesity, which has been implicated as a metabolically active depot, conferring higher risk for the development of CVD. Thus, the finding that WC is highly correlated with CRP in this population is not surprising.

While our findings are novel and extend the current literature regarding low-grade inflammation in the SCI population, our study is not without limitations. The cross-sectional design makes predictions as to the CVD prognostic value of CRP difficult. Prospective studies, such as those previously described in the able-bodied population,^{10,11} are needed to elucidate the value of CRP for predicting cardiovascular events in this population. Our sample population was also limited by the fact that it included only 13 women; subanalysis by gender did not yield significant results. Nevertheless, our data indicate that chronic SCI, particularly tetraplegia, is associated with a unique risk profile for CVD. Coupled with the increased fat mass in persons with tetraplegia, our findings may explain the previously reported higher risk for CVD in persons with tetraplegia over those with paraplegia.

In conclusion, mean CRP levels of our community-dwelling sample population of men and women with chronic SCI are consistent with the AHA classification of high CVD risk. However, tetraplegia is associated with significantly higher CRP levels than paraplegia. WC and level of lesion were independently associated with CRP, suggesting that those with tetraplegia and elevated WC may be at particularly high risk of CVD. The relationship between CRP

and cardiovascular events requires elucidation in this population.

Acknowledgements

We thank the participants of the SHAPE SCI study and Rebecca Bassett and Iwona Chudzick for their help with data collection. The study was funded by the Canadian Institutes for Health Research.

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