Cardiometabolic Risk Profiles in Pre- Versus Postmenopausal Women With Spinal Cord Injury: Preliminary Findings

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Objective: To compare the cardiometabolic risk (CMR) profile of premenopausal and postmenopausal women with spinal cord injury (SCI). **Method**: Post hoc analysis of a multicenter cross-sectional study assessing CMR. Seventeen women with ASIA Impairment Scale (AIS) A or B SCI between C5 and T12 were stratified into 2 groups according to menopausal status (11 premenopausal vs 6 postmenopausal women). Data collected included demographic, social, medical, menopausal, hormone use, and menstrual histories. Assessments included physical, anthropometric, and blood pressure measures; fasting serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and hemoglobin A1C (Hb1Ac); calculated low-density lipoprotein (LDL-C); and an oral glucose tolerance test. **Results:** The premenopausal group had a mean age of 32.4 years compared with 56.0 years in the postmenopausal group. Similar group findings included body mass index (BMI) (22.4 vs 22.2), HDL-C (52.5 vs 53 mg/dL), HbA1c (4.9 vs 5.1%), fasting blood glucose (FBG) (79.3 vs 84.8 mg/dL), and systolic blood pressure (SBP) (104.6 vs 111.8 mm Hg). TG, TC and LDL-C were significantly higher in postmenopausal group (55.7 vs 101.8 mg/dL, $P = .01$; 158.3 vs 191.6 mg/dL, $P = .04$; 94.7 vs 118.2 mg/dL, $P = .04$). **Conclusions:** The findings from this study suggest that postmenopausal women with SCI have CMR trends similar to those observed in nondisabled women, characterized by increases in TG, TC, and LDL-C despite favorable BMIs and glycemic indices. Even though the present study includes significant limitations, future evidence may also suggest that heightened surveillance and guideline-driven interventions are indicated for perimenopausal and postmenopausal women with SCI. **Key words:** *cardiometabolic risk, menopause, spinal cord injury*

All-cause cardiovascular disease (CVD) is the most frequent cause of death in the aging spinal cord injury (SCI) population,[1,2] representing 46% of deaths in people who have been injured for longer than 30 years and 35% of deaths in people with SCI over 60 years of age.[3] When compared with the nondisabled general population, Garshick found that people with SCI had excess mortality due to CVD (relative risk [RR], 3.66).[2] Similarly, DeVivo et al reported an elevated risk of ischemic heart disease in people with SCI (standardized mortality ratio [SMR], 1.6 for males and 1.9 for females).[4] These data indicate that persons with SCI may be living long enough to develop chronic diseases and that CVD risk appears to be elevated.[4] This altered trajectory of CVD risk raises the question of whether people with SCI may have unique clusters of cardiometabolic risk factors that impart a health hazard beyond that observed in the general population.

Nash and Mendez also examined cardiometabolic risk (CMR) clustering,[5,6] utilizing National Cholesterol Education Project (NCEP) Adult Treatment Panel (ATP) III guidelines in persons with SCI. The authors found that the combination of 3 risks from among 5 identified CMRs – abdominal obesity, elevated fasting triglycerides (TG), low levels of high-density lipoprotein (HDL-C), hypertension, and fasting hyperglycemia (FBG) – conferred a diagnosis of cardiometabolic syndrome in more than 1 of 3 young, healthy persons with paraplegia.[5] Groah and Nash recently reported on 121 subjects with SCI and found that overweight/obesity, low-density lipoprotein (LDL-C), HDL-C, hypertension, and elevated total cholesterol (TC) were the most frequent cardiometabolic risk factors in people with chronic SCI.[6] These findings were similar to those reported by Wahman et al in a highly inbred

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Swedish population of persons with paraplegia.[7] Risk clustering differed by level of injury, with persons with tetraplegia having greater risk for disorders involving carbohydrate metabolism than those with paraplegia and persons with paraplegia having greater risk of hypertension[8] and dyslipidemia.[9] This is consistent with previous evidence of differential CVD risk by level and completeness of SCI.[10]

Despite reports of multiple CVD risks in the SCI population, obesity remains the most frequently occurring risk factor among persons with tetraplegia (70.8%) and paraplegia (75.3%).[9] Likely related to a high prevalence of obesity,[10,11] this population demonstrates a higher prevalence of insulin resistance (ISI_O),[12] diabetes mellitus,[5,13] dyslipidemia,[3,14] inflammation,[15] and elevated C-reactive protein (CRP),[12,16] which may account for the elevated CVD in long-term survivors with SCI.[1,2]

Estrogen exerts an overall protective effect on cardiometabolic risk through its functions of lowering serum glucose levels and increasing insulin secretion, HDL-C, and hepatic proteins.[17,18] In nondisabled women, the average age of onset for menopause at which point estrogen levels permanently decline is 51 years old (range, 45-55 years).[19] Postmenopausal women not using hormone replacement therapies (HRT) have a 15% increased prevalence of metabolic syndrome as a result of these hormone changes.[20] The reduced estrogen levels lead to weight gain and altered fat distribution,[21] such that increases in abdominal adiposity significantly correlate with increased CRP,[22,23] CVD risk,[24] coronary atherosclerosis,[25] and CVD mortality.[26] Moreover, increases in total cholesterol (TC) and LDL-C are associated with menopausal states independently of age, body mass index (BMI), and ethnicity,[27,28] with the greatest changes to lipid profiles occurring during the year around the final menstrual period (FMP).[28] There is also an increased postmenopause incidence of coronary artery disease (CAD), atherosclerosis, and myocardial infarction,[18] with the best predictor of future coronary events and CVD death being the ratio of total cholesterol to HDL-C (TC:HDL).[29] The number of years since the cessation of menses independently relates to the carotid intima-media thickness (C-IMT) and directly links menopause to CAD and other endpoints for CVD.[30,31]

Although our understanding of cardiometabolic risk is fairly robust for men with SCI, there has been a paucity of research examining cardiometabolic risk in women with SCI.[4] Studies specifically examining menopause in SCI women tend to focus more on subjective symptoms as opposed to accelerated disease risks.[32,33] More people are living to older ages with SCI, menopause occurs earlier in women with SCI (mean age, 43.3 years),[34] and 7.9% of women have permanent cessation of menses as a result of injury,[34] therefore more detailed investigation of this population is warranted. Hence, the purpose of this study is to describe cardiometabolic risk (CMR) by menopausal status in a population of women with SCI.

Methods

This is a post hoc analysis of a multicenter cross-sectional study examining CMR factors in 121 individuals with chronic ASIA Impairment Scale (AIS) A or B SCI.[6] Data from all women enrolled in the study (N=26) were abstracted and supplemented with a written questionnaire and phone interview examining women's health issues. Seventeen of the 26 female subjects participated in the present study. The study was approved by the institutional review boards at both study sites. Informed consent was obtained prior to entry into the study.

General health history assessment

After subjects gave consent for study participation, a brief medical history was conducted using a structured questionnaire and included demographic information, previous surgeries, current and previous medications, current and past smoking status, and history of CVD and diabetes. Relevant family history for CVD was also collected. Level of injury and AIS[35] classification were confirmed by a brief exam according to established standards.[35]

Women's health history assessment

To obtain data on women's health history, participants were mailed questionnaires regarding

health, menopausal, and relevant medication histories. Data on family history, demographic information, and any chronic medical conditions were collected, including history of any thromboembolic events both before and after SCI. The menstrual history questionnaire presented questions on menstrual status, dysmenorrhea, pain, menorrhagia, metrorrhagia, oligomenorrhea, and polycystic ovary syndrome, as well as any physician visits and recommendations that were associated with these conditions. Difficulties associated with pregnancies included interrupted pregnancy, miscarriage, high blood sugar or high blood pressure, chronic pain or fatigue, clotting, and heavy bleeding. Difficulties with labor and delivery included preterm labor, hemorrhage, prolonged labor, infection, fever, or the arrest of active labor. The medications table contained a list of relevant medications such as oral contraceptives or those often prescribed for treatment of adverse symptoms of menopause. Again, patients were asked to describe medication use both before and after their injury. The participants were also contacted via telephone to facilitate survey completion.

CMR risk assessment: lipid profile and risk standards

Plasma TC, HDL-C, and triglycerides (TG) were assayed on an automated analyzer (Roche Cobas-Mira) utilizing commercially available kits according to manufacturer's instructions and run procedures. Samples were centrifuged and stored at –70°C and then mailed monthly to the Core Laboratory at the University of Miami School of Medicine. LDL-C was calculated using the method of Friedewald[6,36]:

$$\text{LDL-C} = \text{TC} - [(\text{fasting TG} \div 5) - \text{HDL-C}].$$

Blood glucose was measured on fresh samples using the glucose oxidase method. An oral glucose tolerance test was then administered. The subject was instructed to consume 75 g of a glucose solution after 12 hours of fasting with no smoking, strenuous exercise, alcohol, or caffeine for 24 hours before the blood draws. A second blood sample was taken 2 hours later from a second venipuncture.[6] These samples were processed and stored following the same process as outlined for lipids (see above). Glycated hemoglobin (HbA1c) was assayed at the Washington Hospital Center.[6,37,38] BMI was measured after assessing supine height and body mass, the latter on a calibrated scale. BMI was computed as body mass (kg) x height (m^{-2}). Major risk factors were classified according to *Third Report of the National Cholesterol Education Panel ATP III* .[37]

Analyses

Subjects were stratified according to menopausal status, defined as either pre- or postmenopausal at the time of their testing. Demographic data were analyzed for each group by calculating means and standard deviation (*SD*) for age and BMI. The Mann-Whitney *U* nonparametric test was used for comparing CMR factors in pre- and postmenopausal women with SCI. Categorical variables analyzed included ethnicity and hormone drug use. The level of significance was determined a priori at the $P \leq .05$ level.

Results

Health history and demographics are shown in **Table 1**. There were 11 women in the premenopausal group and 6 in the postmenopausal group. Mean age of the premenopausal group was 32 years (±10 years; range, 19-45) compared with 56 years (±9.4 years; range, 48-73) in the postmenopausal group. In the premenopausal group, 6 women were white, 3 were African American, and 2 were "other"; there was 1 person with tetraplegia, 11 with paraplegia, 5 with AIS A SCI, and 6 with AIS B SCI. Three reported a family history of CVD and a history of tobacco use.

In the postmenopausal group, 4 women were white, 1 African American, and 1 "other"; there were 3 persons with tetraplegia, 3 with paraplegia, 4 women with AIS A SCI, and 2 with AIS B SCI. The mean age at the time of menopause was 43 years (range, 40-46 years). Three of these women reported a family history of CVD, whereas only 1 woman reported tobacco use.

Table 1. Health history and demographics

Health history information	Premenopausal (n=11)	Postmenopausal (n=6)
Mean age ± *SD*	32.4 ± 10.0	56.0 ± 9.4
Mean age at time of menopause[a] (range)		43.8 (40-46)
Ethnicity, n		
White	6	4
African American	3	1
Other	2	1
AIS, n		
A	5	4
B	6	2
Tetra	1	3
Para	10	3
Family history of CVD, n	3	3
Reported tobacco use, n	3	1

Note: CVD = cardiovascular disease; AIS = ASIA Impairment Scale.
[a]Permanent cessation of menses.

Table 2. Natural and medical history

	Premenopausal (n=11)	Postmenopausal (n=6)
Oral contraceptive use	6	2
Before injury	4	0
After injury	0	2
Both before and after injury	2	0
HRT use	0	4
Before injury		1
After injury		2
Both before and after injury		1
Menopausal occurrence		
Naturally before injury		2
Naturally after injury		3
Surgically before injury		0
Surgically after injury		1

Note: HRT = hormone replacement therapy.

Women's health history assessment

As shown in **Table 2**, of the 17 women included in this study, only 6 had gone through menopause at the time of the study: 1 woman with tetraplegia went through menopause before her injury, 1 woman with tetraplegia was injured during her perimenopausal transition, 3 women with paraplegia went through menopause after their injury, and 1 woman with tetraplegia had a partial hysterectomy to end her menstruation after injury. Four of the 6 postmenopausal women have used, or were using, hormone replacement therapies (HRT) at the time of study. Of the 11 menstruating women, 8 continue to have a regular cycle and 3 reported a problem with frequency and regularity of their cycles.

Cardiometabolic risk assessment: lipid profile and risk standards

Table 3 shows CMR factors by menopausal status. CMR data from 1 postmenopausal woman was excluded due to exceptionally high HDL-C

Table 3. CMR risk factors and lipid profiles by menopausal status

Variable	Premenopausal (n=11) Mean ± *SD* (range)	Postmenopausal (n=6) Mean ± *SD* (range)	Recommended values
Age	32.36 ± 10.01 (19-47)	56.4 ± 10.407 (48-73)	
BMI	22.36 ± 5.69 (16-37)	22.2 ± 5.805 (17-31)	<22 kg/m^2 [a]
SBP	104.64 ± 17.24 (88-142)	111.75 ± 30.467 (76-150)	≤120 mmHg
TC	158.27 ± 28.46 (120-202)	191.6 ± 20.18 (162-211)	<200 mg/dL
HDL	52.45 ± 16.75 (29-89)	53 ± 9.924 (43-66)	>50 mg/dL
TC:HDL	3.1795 ± .736 (2.21-4.39)	3.748 ± .952 (2.72-4.74)	<4.5
TG	55.727 ± 13.44 (31-72)	101.8 ± 44.695 (64-154)	<150 mg/dL
Calculated Framingham risk points	1.045 ± .522 (.5-2)	4 ± 5.656 (1-14)	
LDL	94.727 ± 22.8389 (69-144)	118.2 ± 22.818 (92-148)	<100 mg/dL
FBG	79.273 ± 9.42 (67-94)	84.8 ± 4.658 (80-91)	<100 mg/dL (normal) 100-125 mg/dL (impaired) ≥126 mg/dL (diabetes)
Hb1Ac	4.85 ± .42 (4.3-5.8)	5.14 ± .23 (4.9-5.5)	4.4%-6.4 %
Insulin Sensitivity Index	7.28 ± 4.82 (3-18.8)	5.18 ± 2.616 (3-9.4)	<20 μIU/mL
History of thromboembolic event	2	1	

Note: BMI = body mass index; CMR = cardiometabolic risk; FBG = fasting blood glucose; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TC:HDL = ratio of TC to HDL; TG = triglycerides.
[a]Laughton, 2009[51]

(103 mg/dL). Exclusion of this outlier did not have any effect on trends or significance. A significantly larger proportion of the group of postmenopausal women had higher TC (mean = 191.6 and 158.3 mg/dL; $P = .05$), TG (mean = 101.8 and 55.7 mg/dL; $P = .01$), and LDL-C (mean = 118.2 and 94.7 mg/dL; $P = .05$) values. The postmenopausal women had higher, though nonsignificant, elevation of SBP (mean = 111.8 and 104.6 mm Hg), HDL-C (mean = 53 and 52.5 mg/dL), TC:HDL (mean = 3.75 and 3.18 mg/dL), Framingham Risk (average number of factors, 4 and 1.05), FBG (mean = 84.8 and 79.3 mg/dL), and Hb1Ac (mean = 5.14% and 4.85%).

Discussion

This study provides preliminary evidence that women with SCI may have comparable trends in CMR as those observed in nondisabled women of similar menopausal status. Although mean levels of TC (191.6 mg/dL), TG (101.8 mg/dL), and LDL-C (118.2 mg/dL) were higher in postmenopausal women than those in the

premenopausal group, it is important to note that only LDL-C in postmenopausal women fell above the recommended value. These findings suggest that women with SCI may have increased CMR associated with menopausal status similar to nondisabled women.

All-cause cardiovascular disease is the leading cause of death in women in the United States, with upwards of 50% of all women dying from atherosclerotic-related processes.[39] In the Framingham Heart study,[40] only 6 of the 1,600 premenopausal women who were studied died of coronary heart disease (CHD). However, once the female participants entered menopause, the incidence rates for CHD rose significantly to equal those of age-matched men.[40] Increased menopausal risks include those of dyslipidemia, where higher serum levels of TC, TG, and LDL-C have been observed in menopausal women from North America,[26,28,41] Czechoslovakia,[42] South America,[43] Europe,[44-47] Korea,[16] and Japan.[48] Increases in TC and LDL-C concentrations accompanying menopausal transition remain elevated throughout the lifespan and are independent of age or years post menopause.[28] These results parallel those of the present study wherein postmenopausal women with SCI had higher concentrations of TC, LDL-C, and TG than their premenopausal cohorts.

Among the many isolated lipid risks for CVD, elevated TG is positively correlated with coronary heart disease risk solely in women.[39] In the present study, postmenopausal women had higher TG levels (101.8 mg/dL) than premenopausal women (55.7 mg/dL; $P = .011$). Although neither group of women had TG levels near the risk criterion of ≥150 mg/dL, the higher level for postmenopausal women suggests that there could be a trend associated with menopausal status and in certain situations clinicians may consider heightened surveillance.

Likewise, postmenopausal status typically carries with it an increase in LDL-C (8.2 mg/dL higher LDL-C in one report[49]). The offspring Framingham Heart study examining menopausal status and lipid levels in nondisabled women demonstrated that postmenopausal women had higher TG (124 vs 83 mg/dL; $P = .0001$), TC (229 vs 193 mg/dL; $P = .0001$), TC:HDL-C (4.4 vs 3.6 mg/dL; $P = .0001$), and LDL-C (146 vs 118 mg/dL; $P = .0001$),[50] which the authors suggest is due to the increasing androgen to estrogen ratio that occurs when estrogen levels decline. Although the present study observed smaller group differences for TG, TC, and LDL-C, trends mirror those of the offspring study and favor higher risks for atherosclerotic disease in both the nondisabled and SCI populations.

Although considerable information has documented elevated CVD risk in nondisabled postmenopausal women, little information is known about CVD risk and menopausal status in women with SCI. The few studies on CVD in women with SCI neglect to account for menopausal status as a variable. Storch et al reported that premenopausal women with SCI were protected to a greater degree than men with SCI from adverse lipoprotein profiles and adverse CVD risks, a finding attributed to their estrogen levels.[45] However, their study failed to examine peri- and postmenopausal women and primarily focused on risks of men with SCI.

In a multicenter study of women's self-reported reproductive health after SCI by Jackson et al, 472 women were interviewed.[34] Jackson et al found that the average age for menopause after injury was 43.3 compared to 45.5 years for those going through menopause prior to injury.[34] The results of the present study mirror the results from Jackson et al, wherein the average age of menopause post injury was 43.8 years (range, 40-46). Jackson et al also found that, of the women who went through menopause post injury, 14.5% went through menopause within 1 year post injury.[34] These data suggest that women with SCI who experience earlier than anticipated menopause may be at risk for earlier onset CMR and CVD.

BMI is not an accurate estimate of body fat in the SCI population[51] and, as a result, its predictive value is questionable. Laughton's adjusted BMI for SCI that classifies those with BMI >22 kg/m^2 as overweight or obese was utilized as a more accurate body composition modeling.[51] Given that the average BMI is 24.58 kg/m^2 for premenopausal women and 26.13 for postmenopausal women without SCI in the United States,[50] and approximately 68% of persons with

SCI are above the 22 kg/m^2 cutoff,[52] BMIs in both the premenopausal (mean BMI, 22.4 kg/m^2) and postmenopausal (mean BMI, 22.2 kg/m^2) women with SCI were lower than would be anticipated.

These study results should be considered preliminary, given several limitations that are largely driven by sample size issues. First, the sample size of 17 does not allow for subgroup comparisons (eg, persons with tetraplegia vs paraplegia) nor controlling for confounders such as age, level of injury, duration of injury, and completeness of injury. There may have been variances in outcomes such as blood pressure, cholesterol, BMI, or others based on level of injury, but these could not be elucidated with just 17 subjects. Although we recognize that BMI is unstable and a questionable predictor of CVD risk in the SCI population,[51] we felt that it was important to include it because very little data has been reported on CMR in women with SCI. Finally, even though CMR and lipid levels represent predictors of CMR, surrogates that reflect disease progression after SCI such as carotid intima-media thickness and coronary artery calcium scoring may better reflect actual disease risk. It is also important to note that this study does not aim to compare CMR in women with SCI versus those without SCI; it is meant as a point of departure for future investigations of CMR within the population of women with SCI. It should also be acknowledged that in this study group comparisons were made on 11 dependent variables. With a traditional Bonferroni correction to be implemented, no difference would be acceptable unless the *P* value was smaller than .05/11 or .0045. This limitation needs to be considered when interpreting the current findings among similar studies once they become available.

In conclusion, this preliminary study suggests that postmenopausal women with SCI may experience a similar adverse trend in CMR as observed in nondisabled women. These findings provide early evidence that additional study and disease surveillance of this underrepresented population may be warranted, especially in the context of an earlier transition to menopause and the heightened risk and subsequent functional implications of this and other secondary conditions in people with SCI.

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