The impact of individual's sex and gender on the outcomes spinal cord injury: An update from bench to bedside

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OBJECTIVES

1. Provide an overview of the sex and gender distribution in individuals with SCI, and the changes related to an aging population;
2. Review the literature on the sex-related differences in the outcomes in experimental studies using animal SCI models;
3. Summarize the literature on the influence of sex and gender as a key determinant for access to care and outcomes following traumatic SCI

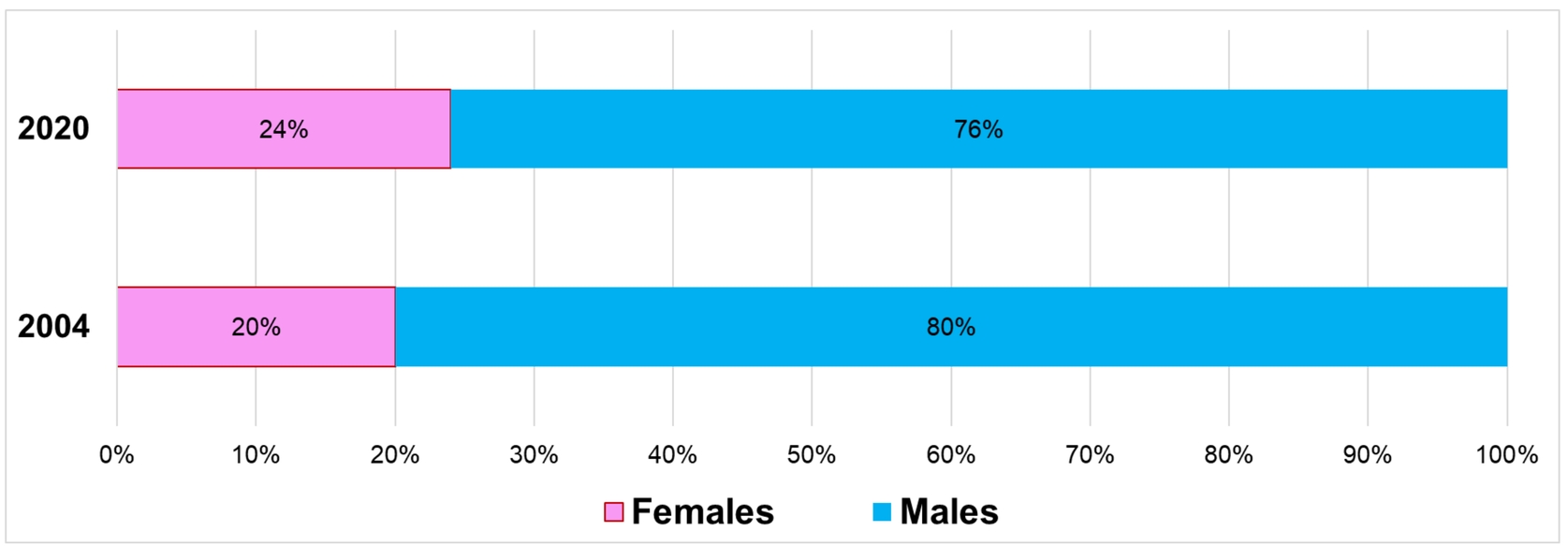
EPIDEMIOLOGY OF TRAUMATIC SPINAL CORD INJURY

The worldwide incidence of traumatic spinal cord injury (SCI) varies from 6.2 to 174 per million inhabitants yearly (Furlan et al, Can J Neurol Sci, 2013; 40(4):456-64). The estimated lifetime economic burden per individual with SCI in Canada varies from $2,105,811 to $3,06,028 Canadian dollars (Krueger et al, Chronic Dis Inj Can, 2013; 33(3):113-122). While the incidence of SCI is relatively low, the economic impact of this condition is substantial.

The epidemiology of SCI has been changing over the past three decades. Based on data from a large database from the United States, age at the time of SCI has increased from 28.7 years in the 1970s to 42.2 years between 2010 and 2014. This aging phenomenon was observed in both sexes and all ethical groups (Chen et al, Arch Phys Med Rehabil, 2016; 97(10):1610-1619). An aging population has led to an increase in fall-related SCIs world-wide.

Over time there has been an increase in the proportion of females sustaining a traumatic SCI. Data from the Canadian Rick Hansen SCI Registry (RHSCIR) illustrates a gradual increase in females sustaining traumatic SCI (**Figure 1**). There is no difference between males and females in terms of age at time of injury or mechanism of injury. Similar trends are seen in other countries and these trends are expected to continue in the future.

Figure 1. Overtime change in the epidemiology of females and males with SCI .



Less is known about the effects of gender, which refers to socially constructed roles, behaviors, expressions and identities of girls, women, boys, men, and gender diverse people (CIHR website). Future research should include a gender-sensitive research framework for SCI and include both sex and gender (Raguindin et al, Maturitas, 2021; 147:14-18. 2021). The International SCI Core Data Set (version 3.0) have clarified sex and gender (https://www.iscos.org.uk/international-sci-core-data-sets).

PRECLINICAL DATA

The estrogen-mediated neuroprotection has been supported by preclinical data. In an experimental animal study, administration of 17beta-estradiol to ovariectomized rats improved motor recover, increased white matter sparing, and decreased apoptosis in post- and pre-menopausal rats. Also, ovary-intact 1-year-old rats had less favorable recovery than ovary-intact 2-month-old rats, suggesting that endogenous estrogen confers neuroprotection in young rats, which is lost in older animals (Chaovipoch P et al, J Neurotrauma. 2006; 23(6):830-852).

Testosterone can be aromatized to 17beta-estradiol and may increase estrogen-mediated protection. Further, testosterone has been shown to increase excitotoxicity in models of CNS injury. In another experimental study, administration of 17beta-estradiol to male rats improved their locomotion, increased neuronal survival, reduced apoptosis, and increased white-matter sparing. In the absence of endogenous androgens, SCI induced greater apoptosis, administration of 17beta-estradiol reduced apoptosis to the same extent in gonadectomized and gonad-intact male rats. These data suggest that delayed post-SCI administration of a clinically relevant dose of 17beta-estradiol is protective in male rats, and endogenous androgens do not significantly affect estrogen-mediated protection (Kachadroka S et al, J Neurotrauma. 2010; 27(3): 611-626).

The results of a recent study using a larger sample size also suggest better outcomes in female animals after taking into consideration discrepancies in age and weight of the animals across sexes (Datto J et al, Neural Regen Res 2015; 10(10): 1533-1536).

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CLINICAL DATA

While few pre-clinical studies documented potential neuroprotective effects of estrogen and progesterone, there is no conclusive evidence on sex-related differences in outcomes after traumatic SCI.

A recent study examined the potential effects of sex on injury epidemiology, management and outcomes after traumatic C1-L2 SCI using prospectively accrued data from a large Canadian database.

Data were obtained from the Rick Hansen Spinal Cord Injury Registry (RHSCIR), which includes 18 acute care and 13 tertiary rehabilitation hospitals across Canada. The RHSCIR is a prospective observational database that collects data from consenting individuals who have sustained a new traumatic SCI from April 2014 to September 2019. All participating sites obtained REB approval prior to enrolling participants. Further information the ethical and jurisdiction issues related to RHSCIR was published by Noonan VK, et al. (Health Policy 2013; 8(4):87-99).

A series of propensity-score matched cohort studies was performed comparing the subgroups of females in premenopause (younger than 40 years of age), females in perimenopause (between 40 and 50 years of age) and females in postmenopause (older than 50 years of age), with the subgroups of males distributed similar age categories.

In each subgroup analyses, females were matched on a 1:1 ratio to males using the propensity score matching on age at SCI onset, Charlson Comorbidity Index, and level and severity of SCI.

Of the 7,196 cases included in the RHSCIR, 1,245 females and 4,334 males fulfilled the inclusion and exclusion for this study and they were considered during the propensity-score matching process.

SUMMARY OF THE BASELINE DATA

Figure 1. Comparisons between females and males living with traumatic SCI with regard to their baseline data.

Variables	Females n=1,245	Males n=4,334	p Value
Age at injury (years): median (range)	53 (14, 96)	49 (12, 98)	<0.0001
Age by group: n (%)			0.0015
Younger than 40 years of age	408 (32.9%)	1613 (37.3%)	
Between 40 and 50 years of age	174 (14.0%)	666 (15.4%)	
Older than 50 years of age	660 (53.1%)	2050 (47.4%)	
Ethnical groups: n (%)			0.0006
White	542 (84.0%)	1986 (83.0%)	
Aboriginal	43 (6.7%)	96 (4.0%)	
Asian	39 (6.0%)	156 (6.5%)	
Other groups	21 (3.3%)	156 (6.5%)	
Mechanism of injury: n (%)			<0.0001
Fall	678 (55.4%)	1881 (44.1%)	
Transportation	370 (30.3%)	1282 (30.1%)	
Sports	110 (9.0%)	688 (16.1%)	
Other causes	65 (5.3%)	414 (9.7%)	
Charlson Comorbidity Index: n (%)			0.9052
0	689 (65.8%)	2383 (66.0%)	
1 or 2	283 (27.0%)	959 (26.5%)	
3 or more	75 (7.2%)	271 (7.5%)	
Severity of Injury: n (%)			0.0023
AIS A	354 (29.6%)	1478 (35.3%)	
AIS B	102 (8.5%)	353 (8.4%)	
AIS C	233 (19.5%)	767 (18.3%)	
AIS D	508 (42.4%)	1588 (37.9%)	
Injury Level: n (%)			0.9757
Cervical (C1-C8)	820 (67.1%)	2848 (66.8%)	
High-thoracic levels (T1-T6)	108 (8.8%)	384 (9.0%)	
Low-thoracic & high-lumbar (T7-L2)	294 (24.1%)	1031 (24.2%)	

PROPENSITY-SCORE MATCHED COHORT STUDIES

- **Among individuals younger than 40 years of age**, females (n=320) more often were white (p=0.0268) and had SCI due to falls or transportation-related accidents (p=0.0014) than males (n=320), but both subgroups were comparable regarding Glasgow Coma Score and Injury Severity Score. Both subgroups under 40 had comparable management except for females had more often surgical treatment (p=0.0326). There were no significant differences between females and males under 40 regarding outcomes.
- **Among individuals between 40 and 50 years of age**, females (n=133) were alike to males (n=133) regarding the other baseline data, management, and outcomes.
- **Among individuals older than 50 years of age**, females (n=531) had more often fall-related SCIs than males (n=531). Females had shorter LOS in the rehabilitation facilities than males (p=0.0205). However, there were no significant differences between the subgroup of females and the subgroup of males regarding the other baseline data, management, and outcomes.

CONCLUSIONS

- Over time there have been sex-related changes in the epidemiology of traumatic SCI.
- Pre-clinical data suggest effects of sex hormones on outcomes after traumatic SCI.
- However, clinical data do not endorse major sex-related differences in the outcomes after traumatic SCI.