Allostatic Load and Spinal Cord Injury: Review of Existing Research and Preliminary Data

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Objective: To introduce allostatic load (AL) as a framework for measuring stress-related outcomes after spinal cord injury (SCI) by identifying the number and nature of biomarkers investigated in existing studies and by generating preliminary data on AL in 30 persons with traumatic SCI. **Methods:** This systematic review and pilot study were conducted at a medical university in the southeastern United States. A review of literature published between 1993 and 2012 identified studies using 2 or more of 5 classes of AL biomarkers. We then collected data on 11 biomarkers (n = 30) from self-selected participants using physical exams and blood and urine specimen collection. These included waist to hip ratio, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, dihydroepiandrosterone, glycosylated hemoglobin, C-reactive protein, interleukin-6, and cortisol, norepinephrine, and epinephrine normalized by 12-hour creatinine. **Results:** We were unable to identify any studies investigating AL biomarkers from each of the 5 areas or any studies specifically proposing to investigate AL. AL scores were relatively low, with metabolic indicators being the most elevated and neuroendocrine the least elevated. **Conclusion:** AL is a promising, yet underutilized, construct that may be feasibly assessed after SCI. **Key words:** *allostasis, allostatic load, spinal cord injury, stress*

Traumatic spinal cord injury (SCI) typically results in permanent disability and increased risk of health complications and early mortality. In the United States, the primary causes of SCI are motor vehicle crashes, falls, acts of violence, sports, and other unknown etiology.[1] After traumatic SCI, individuals face significant physiological and psychological adjustments.[2,3] Their response to these and other stressors is influenced greatly by the condition of their body (ie, severity of injury, physical conditioning, presence of comorbidities or risk factors for disease, etc) and how they perceive and interpret the situation (ie, coping styles).[4]

The traumatic, sudden nature of SCI and the resulting long-term increased vulnerability to secondary health conditions[5] suggest the appropriateness of evaluating both physiological and psychological stress paradigms among persons with SCI. Some research has suggested that SCI is associated with posttraumatic stress disorder (PTSD),[6-9] although other research has suggested that PTSD rarely occurs in the absence of a depressive disorder.[10] A number of studies have examined psychological adjustment to SCI,[2,3,11] but further research regarding physiological responses to injury and stressors is warranted.

Two concepts, allostasis and allostatic load (AL), relate to the physiological adaptation to stress and associated costs on the body and brain.[4] Allostasis refers to the dynamic regulatory process by which stability is maintained through changes in physiologic systems including autonomic, central nervous, neuroendocrine, cardiovascular, metabolic, and immune systems.[12] AL is a measure of the "wear and tear" experienced after chronic allostatic responses to stressful situations; it is the price of adaptation.[13] AL may result from recurrent stress and subsequent activation of allostatic systems, failure to shut down the allostatic activity

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following a stressor, or an inadequate response of an allostatic system ultimately leading to elevated activity of another system.[4] The AL model,[14] a biologic theory of stress, proposes that the stress response is influenced by a number of factors, including life experiences, genetics, and behavior. Over time, the accumulation of AL can have systemwide adverse effects, contributing to morbidity and mortality.[14-17]

Measurement of AL was initially operationalized to reflect levels of physiologic activity across the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, the cardiovascular system, and metabolic processes through a set of 10 biomarkers, each having been previously linked to increased risk for pathology.[4,15] A more diverse and expanded set of biomarkers have since been grouped by (1) anthropometric measures and (2) cardiovascular and respiratory, (3) metabolic, (4) neuroendocrine, and (5) immune system biomarkers.[18] In the original index, immune biomarkers were not assessed. A review by Juster et al[18] lists 25 biomarkers commonly assessed in AL studies. The number of markers measured in any particular study ranges from 4 to 17.[18] Numerous algorithms, formulas, and statistical techniques have been implemented to quantify, or score, AL based on the biomarkers collected. Each biomarker contributes to an overall risk score defined by a critical threshold or cutoff point, whereas the biomarker only counts for the overall score if it is outside the critical threshold.

It is possible that specific stressors associated with long-term injury, in combination with daily life stressors, may make persons with SCI more susceptible to high levels of AL. In studies assessing biomarkers in persons with SCI, there has not been consistency in which biomarkers were assessed or in the cutpoints for some biomarkers. As persons with SCI are at increased risk of secondary conditions and early mortality due to their injury, increased AL is an important concept that could result in even further negative health consequences due to the cumulative wear and tear on body systems and secondary health conditions.

Summary and Purpose

We were unable to identify any studies that explicitly utilized the construct of AL to organize outcome measures in studies of SCI. Therefore, we performed a systematic review to identify studies measuring 2 or more of the 5 categories of biomarkers used to measure AL, so as to identify studies that implicitly measure components of AL. By identifying the biomarkers most widely used in SCI research, we have highlighted gaps in the literature related to the most widely used AL parameters. (It is beyond the scope of this article to review specific findings.)

Our secondary purpose was to generate preliminary data from 30 participants using 11 AL parameters, providing preliminary data on relative frequency of each indicator. This may help to guide future research establishing quartile scores that may be used as potential cutpoints, parameters for power analyses, and selection of specific measures.

Stage I: Systematic Review

A systematic review of literature was conducted using the following databases: PubMed and Cumulative Index to Nursing and Allied Health Literature Plus (CINAHL Plus) through EBSCOhost. The search strategy paired MeSH terms ("spinal cord injuries") and text words ("cross-sectional studies") with each of the biomarkers previously indicated in AL literature. The original 10 biomarkers of AL included waist to hip ratio (WHR), systolic and diastolic blood pressure (SBP, DBP), dihydroepiandrosterone sulfate (DHEA-s), cortisol, norepinephrine (NE), epinephrine (Epi), high-density lipoprotein (HDL) cholesterol, total cholesterol to HDL ratio, and glycosylated hemoglobin (HbA1c).[15] Six additional biomarkers, including fibrinogen, interleukin-6 (IL-6), C-reactive protein (CRP), albumin, creatinine clearance, and peak respiratory flow, were added to form an expanded set, which provided a more inclusive evaluation of biological dysregulation.[19] Additional biomarkers have since been assessed. Our literature review focused on the 25 biomarkers repeatedly used in AL studies, as presented by Juster et al.[18]

Table 1. Studies meeting inclusion criteria for assessing individual biomarkers of allostatic load (AL) in SCI populations

Author, year	*N*	Anthropometric	CV and respiratory	Immune	Metabolic	Neuroendocrine	Total AL markers
Zhong, 1995	197	1					3
Janssen, 1997	37	1	2				8
Huang, 2000	47	1				1	2
Kemp, 2000	188	1					6
Manns, 2005	22	1	1	2	6		10
Lee, 2006	93	1		1	7		9
Lee, 2006	168		2		2		4
Bauman, 2007	224	1	2		7		10
Liang, 2007	185	1	2		5		8
Nash, 2007	41	1	2		6		9
Wang, 2007	62	1		2	9		12
Edwards, 2008	31	1		1	7		9
Gibson, 2008	69	2	2	1	7		12
Huang, 2008	42			1	2		3
Finnie, 2008	75	2	2	1	7		12
Liang, 2008	131	1	2	1	3		7
Liang, 2008	129			1	1		2
Morse, 2008	63	1	2	1			4
Buchholz, 2009	76	2	2	1	7		12
Hetz, 2009	75	1			5		6
Laughton, 2009	77	1		1			2
Wang, 2009	110	2	2	1	8		13
Matos, 2010	65	1	2	3	5		11
Gorgey, 2010	10	2			7		9
Garshick, 2011	59	1	1	2			4
Gorgey, 2011	39	1			7		8
Gorgey, 2011	13	1			7		8
Gorgey, 2011	13	1			7		8
Groah, 2011	121	1	2		8		11
Groah, 2011	125	1	2	2	7		12
La Favor, 2011	14	2	2	1	5		10
Lieberman, 2011	38		2		5		7
Lieberman, 2011	38		2		5		7
Wahman, 2011		1	2		3		6
Matos, 2011	34	1	3	3	6		13
Krause, 2008	30	1	2	2	3	3	11

Note: See the supplementary digital content for a more comprehensive table (**Table A1**) (doi: 10.1310/sci2002-137).

Cross-sectional studies published between 1993 (the year that the term allostatic load was coined) and 2012 were included if they met the following characteristics: participants were adults (>18 years) with chronic (>1 year) traumatic SCI and the study assessed at least 1 biomarker of AL from at least 2 groups (anthropometric, cardiovascular and respiratory, metabolic, immune, or neuroendocrine). Case reports, case series, and studies other than cross-sectional analyses and studies published in languages other than English were excluded. Animal studies were also excluded.

The initial selection excluded obviously unrelated articles retrieved by the searches based on the title alone. The excluded studies were reviewed to ensure no potentially appropriate studies were inadvertently removed. The titles and abstracts of selected studies were then further examined for pertinent information. The references of selected articles and previously published systematic

reviews were scanned for applicable articles. Thereafter the articles were evaluated for inclusion and exclusion criteria.

Data were extracted from the selected articles into an electronic data collection form developed for this review that includes information on the study, participants, and outcomes.

Search Results

The PubMed search returned 92 articles, and CINAHL returned 52. Following the selection procedure, we identified 35 studies measuring biomarkers of AL from at least 2 of the 5 groups in individuals with chronic traumatic SCI (**Table 1**). On average, the studies measured 8 biomarkers (range, 2-13) and 3 groups (range, 2-4).

The majority of the studies examined metabolic biomarkers, most often in relation to cardiovascular disease[20-36] or metabolic syndrome risk,[37-39] but also in association to health outcomes or other biomarker levels.[40-42] Immune biomarkers, most commonly CRP, were included in the studies that assessed cardiovascular disease risk, or they were measured as markers of inflammation and associations with other AL biomarkers that were examined.[43-46] Studies gathering anthropometric measures of adiposity in association with other AL biomarkers were also common, although waist circumference was often the measure reported rather than the original AL biomarker WHR.[47-54] Only one study measured a neuroendocrine biomarker of AL in individuals with chronic, traumatic SCI.[47] Investigators have historically focused on examining indicators of health after SCI using either a single biomarker or multiple measures attributed to a specific health outcome (such as bone density, body composition, or cardiovascular risk).

Stage II: Pilot study

Participants

Institutional review board approval was obtained prior to data collection. Participants were 30 self-selected volunteers identified through the South Carolina SCI Association. Inclusion criteria were (1) participant age of at least 18 years old, (2) traumatic SCI with residual impairment, (3) minimum of 2 years post SCI, and (4) ability to travel to the data collection site and participate in the data collection activities.

Procedures

Data were collected over 2 days at a medical university in the southeastern United States. Participants received $250 in remuneration. This included the expense of traveling for the data collection. Eight of the participants required overnight stays, and accommodations were made locally at no cost to the participants. Demographic and injury-specific data were collected on day 1, and participants were provided with the equipment and instructions needed to complete an overnight 12-hour urine collection. They were instructed to begin the urine collection on the evening before their second visit and to bring the urine specimen with them on day 2. The following tests were conducted on day 2 (**Table 2**): (1) SBP and DBP,[55] (2) WHR,[56] (3) blood specimen collection via standard phlebotomy techniques, and (4) urine specimen. We processed the blood for fasting total serum cholesterol, HDL, DHEA, and blood HbA1c, CRP, and IL-6. We processed urinary excretion of cortisol, NE, and Epi, normalized by 12-hour creatinine excretion to adjust for body size and renal function.

Waist to hip circumference was measured by procedures outlined in the 1988 Anthropometric Standardization Reference Manual.[57] Waist circumference was measured at the narrowest point between the ribs and the iliac crest, and the hip circumference was measured at the maximal site around the buttocks. Measurements were taken while the participant was lying down. Blood pressure was measured using the Hypertension Detection and Follow-up Program protocol.[58] Three seated blood pressure readings were completed, and average systolic and diastolic blood pressures were computed from the second and third readings.

Analysis

We used a total of 11 biomarkers, including 9 of the 10 original markers (all except DHEA-s)

Table 2. Biomarkers, cutpoint reference values, and the sources of data

		Biomarkers	Reference value	Data source
Traditional AL	Anthropometric	High WHR	≥0.94	Physical exam
	CV and respiratory	High SBP	≥148 mm Hg	Physical exam
		High DBP	≥83 mm Hg	Physical exam
	Neuroendocrine	High Epi	≥4.99 μg/g creatinine	Urine
		High NE	≥48 μg/g creatinine	Urine
		High cortisol	≥25.69 μg/g creatinine	Urine
		Low DHEA[a]	NA	Serum
		Low DHEA-s[a]	≤350 ng/mL	Serum
	Metabolic	High HbA1c	≥7.10 %	Blood
		Low HDL	≤37 mg/dL	Serum
		High total cholesterol to HDL ratio	≥5.92	Serum
Expanded	Immune	High CRP	≥3.19 μg/mL	Blood
		High IL-6	≥4.64 pg/mL	Blood

Note: CRP = C-reactive protein; CV = cardiovascular; DBP = diastolic blood pressure; DHEA-s = dihydroepiandrosterone sulfate; Epi = epinephrine; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; IL-6 = interleukin-6; NE = norepinephrine; SBP = systolic blood pressure; WHR = waist to hip ratio.

[a]DHEA-s is the sulfated metabolite of DHEA. Stress affects both DHEA and DHEA-s levels, but DHEA-s is typically collected rather than DHEA. We collected DHEA, not DHEA-s, and thus cannot compare to previous allostatic load (AL) reference values.

and 2 relevant immune biomarkers (CRP, IL-6). The addition of these 2 markers follows the later development of the McArthur studies of successful aging and the conclusion that "operationalization of the concept of AL was designed to summarize levels of physiological activity across a range of regulatory systems pertinent to disease risks" and the addition of other markers provides "more comprehensive assessment of cumulative biological dysregulation."[59(1987)] As this study was to generate preliminary data of each of the 5 classes of AL markers, all analyses were descriptive in nature with no attempt to statistically compare AL scores as a function of participant characteristics. Analyses were completed using IBM SPSS software (IBM, Armonk, NY). We calculated overall AL scores, based on traditional cutoff scores reported in the literature, as the criterion cutpoints were taken directly from those listed by Seeman et al.[59] AL was calculated as the sum of indicators where the participant scored above the reference cutpoint outlined in **Table 2**. We also identified the portion of individuals meeting the criteria for each marker (ie, outside the reference value). Quartile scores are reported so that alternative cutoff scores may be considered in future research.

Results

All 30 participants were successfully enrolled, and all appropriate measures were obtained (eg, no cases lacked blood draw). Eighty percent of the participants were male. Sixty percent were non-Hispanic White, 36.7% were non-Hispanic Black, and 3.3% Hispanic. Participants were an average of 45.7 ± 12.5 years of age at time of data collection and 13.8 ± 8.8 years post injury. Because participants were self-selected volunteers from the community, with no hospital records or neurologic assessment to establish the ASIA Impairment Scale (AIS),[60] we characterized SCI severity using self-report methods. Characterizing SCI severity, 43.3% had cervical injuries with no voluntary, functional movement below the level of injury; 30.0% had noncervical, nonfunctional injuries; and 26.7% had functional movement below the level of injury (self-report proxy for the AIS developed and reported in previous studies).[61,62]

Overall AL scores were relatively low, with a mean score of 2.03 (range, 0-5). **Figure 1** summarizes the distribution of scores. **Table 3** summarizes AL scores as a function of demographic and injury characteristics for descriptive purposes.

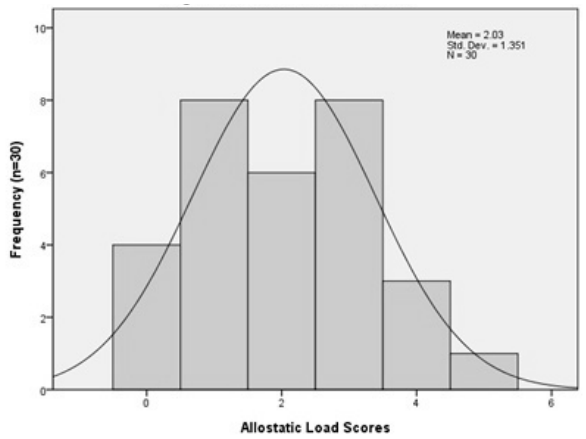

Figure 1. Preliminary data with 30 participants and 5 classes of biomarkers.

The biomarkers with the greatest number of individuals outside the reference values were low HDL (66.7%), WHR (56.7%), and IL-6 (26.7%) (**Table 4**). WHR was the only anthropometric measure collected. Each of the 3 metabolic biomarkers had more than 10% of the participants above the cutoff. Conversely, less than 10% of the participants scored above the criterion value on the remaining 6 parameters, with no participant exceeding the cutoff for high diastolic blood pressure. This included both biomarkers from the cardiovascular and respiratory group and all 3 neuroendocrine measures.

Discussion

We were unable to find any studies that explicitly applied the AL framework with chronic traumatic SCI, and no studies measured biomarkers within each of the 5 general groups. There were, however, 10 studies that utilized at least 4 of the 5 types of biomarkers, most of which used relatively small sample sizes. Neuroendrocrine measures were the least represented followed by immune measures. Therefore, although the AL paradigm has not been explicitly used after SCI, there is potential for applying the framework in multiple studies. The absence of research with AL (physiologic stress framework) is in contrast with a relatively significant number of studies of PTSD,[6,10] which measure psychological response to stress using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*.[63]

This is the first study to utilize the AL framework and report at least one measure of each of the 5 outcome indicators. Perhaps not surprising given the self-selected nature of the participant sample, the results indicated relatively low levels of AL, with substantial variation between differing indicators. WHR, the single anthropometric measure, appeared to be most elevated among the participants, although the use of WHR has been questioned in studies of persons with SCI and is not likely the best indicator of body composition with SCI.[64] Metabolic indicators were the most

Table 3. Allostatic load by participant characteristics.

Characteristic	Median	Mean	*SD*	% AL >0
SCI severity				
Cervical, Non-F (*n*=13)*	3.0	2.54	1.51	84.6
Non-C, Non-F (*n*=9)	2.0	1.89	1.27	88.9
Functional movement (*n*=8)	1.0	1.38	0.92	75.0
Age, years				
18-29 (*n*=8)	2.5	1.88	1.36	75.0
30-44 (*n*=11)	1.0	1.64	1.03	81.8
45+ (*n*=11)	2.0	2.55	1.57	90.9
Years post injury				
1-10 (*n*=12)	2.5	1.92	1.44	75.0
11-15 (*n*=9)	1.0	1.44	0.73	88.9
16+ (*n*=9)	3.0	2.78	1.48	88.9

Note: AL = allostatic load; Non-C = noncervical; Non-F = nonfunctional.

Table 4. Descriptive statistics of individual biomarkers

	Biomarker	Reference value	Mean (*SD*)	25th quartile	50th quartile	75th quartile	% outside reference
Anthropometric	WHR	≥0.94	0.96 (0.13)	0.86	0.96	1.03	56.7
CV and respiratory	SBP	≥148 mm Hg	112.06 (22.29)	98.67	108.00	125.25	6.7
	DBP	≥83 mm Hg	46.64 (6.48)	42.00	47.17	50.75	0
Neuroendocrine	Epi	≥ 4.99 μg/g creatinine	3.13 (0.73)	3.00	3.00	3.00	3.3
	NE	≥48 μg/g creatinine	15.23 (14.71)	10.00	10.00	14.25	3.3
	Cortisol	≥25.69 μg/g creatinine	10.18 (8.73)	5.33	7.06	11.90	3.3
Metabolic	HbA1C	≥7.10 %	5.47 (1.08)	4.95	5.20	5.43	13.3
	HDL	≤37 mg/dL	33.73 (8.40)	28.75	31.00	40.00	66.7
	Total to HDL cholesterol ratio	≥5.92	4.87 (1.14)	4.17	4.71	5.42	16.7
Immune	CRP	≥3.19 μg/mL	1.36 (3.06)	0.25	0.49	1.07	6.7
	IL-6	≥4.64 pg/mL	5.18 (6.71)	1.66	2.70	6.47	26.7

Note: CRP = C-reactive protein; CV = cardiovascular; DBP = diastolic blood pressure; DHEA-s = dihydroepiandrosterone sulfate; Epi = epinephrine; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; IL-6 = interleukin-6; NE = norepinephrine; SBP = systolic blood pressure; WHR = waist to hip ratio.

consistently elevated, showing promise for future AL studies, whereas neuroendocrine measures were the least highly elevated.

Limitations

This study is limited to preliminary data that may help to identify alternative cutpoints for future research. The small sample size precluded statistical comparisons of AL function of demographic and injury characteristics, even though there were trends in the descriptive data. Therefore, no conclusions may be derived regarding AL levels compared with the general population from the current data, although the basis has been established for doing larger scale follow-up studies. There may be inherent aspects of SCI that may invalidate particular AL indicators with SCI. Well-established issues with the autonomic nervous system[65,66] may lead to low prevalence of a particular indicator, such as high diastolic blood pressure (no cases were identified in the current study). Also, SCI is associated with a pattern of secondary conditions that could affect some of the measures. However, this may affect the mechanism by which SCI is associated with a pattern of elevated biomarkers.

Future research

Future research will require larger samples, preferably using population-based cohorts that minimize selection bias based on health or access to treatment. Utilization of a broader number of biomarkers and evaluation of the sensitivity of measures to SCI would help to better quantify AL. Integration of self-report, diagnostic-based indicators (ie, PTSD) and AL biomarkers would provide significant triangulation of methods addressing different types of stress-related conditions. The ultimate utility of stress-based measures would be in their ability to predict future occurrences of secondary health conditions and global health, so that measurement of stress indicators may be used to develop early interventions to improve health and reduce morbidity and excess mortality after SCI.

Conclusion

AL is a promising construct that may feasibly be assessed after SCI with collection of biomarkers. Metabolic indicators appear to be the most significantly elevated among the 5 groups of AL indicators among those with SCI.

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