Inflammatory Stress Effects on Health and Function After Spinal Cord Injury

Crystal M. Noller, PhD,[1] Suzanne L. Groah, MD, MSPH,[2,3] and Mark S. Nash, PhD, FACSM[1,4]

[1]The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, Florida; [2]Paralysis and Recovery Program, MedStar National Rehabilitation Hospital, Washington, DC; [3]Rehabilitation Medicine, Georgetown University Hospital, Washington, DC; [4]Departments of Neurological Surgery and Physical Medicine & Rehabilitation, University of Miami Miller School of Medicine, Miami, Florida

Background: Injury to the spinal cord produces immediate, adaptive inflammatory responses that can exacerbate the initial injury and lead to secondary damage. Thus far, researchers and clinicians have focused on modulating acute inflammation to preserve sensorimotor function. However, this singular approach risks overlooking how chronic inflammation negatively impacts the broader health of persons with a spinal cord injury (SCI). **Objective:** The aim of this monograph was to discuss interrelated processes causing persistent inflammatory stress after SCI, along with associated health risks. We review archetypal factors that contribute to a chronic inflammatory state, including response to injury, acute infection, and autonomic dysreflexia. Secondary complications producing and exacerbating inflammation are also discussed, including pain, depression, obesity, and injury to the integumentary and skeletal systems. Finally, we discuss the role of bacteria and the gut microbiome in this process and then conclude with a discussion on how a pro-inflammatory phenotype promotes an elevated risk for cardiovascular disease after injury. **Conclusions:** Effectively managing chronic inflammation should be a high priority for clinicians and researchers who seek to improve the health and life quality of persons with SCI. Chronic inflammation worsens secondary medical complications and amplifies the risk for cardiometabolic disorders after injury, directly impacting both the quality of life and mortality risk after SCI. Inflammation can worsen pain and depression and even hinder neurological recovery. It is, therefore, imperative that countermeasures to chronic inflammation are routinely considered from the point of initial injury and proceeding throughout the lifespan of the individual with SCI. **Key words**: *cardiometabolic disorders, chronic inflammation, inflammatory stress, spinal cord injury*

Inflammation is the customary adaptive response to injurious stimuli and conditions, including acute infection and tissue damage. Under the best of conditions, the near-term inflammatory response is characterized by activation of host defense against infection, followed by initiation of tissue repair. The inflammatory cascade is typically resolved through integrated feedback mechanisms that restore homeostatic balance. However, when infection or damage persist – or the immune response is directed against the host – chronic inflammation and tissue damage ensue (**Figure 1**). Paradoxically, the chronic inflammatory response may promote ongoing tissue damage while simultaneously engaged in healing and repair. The molecular and cellular actions that constitute simultaneous repair and damage are less well understood than those of acute inflammation. However, prolonged inflammation is now known to be associated with a myriad of disorders that include type 2 diabetes and all-cause cardiovascular diseases. These chronic inflammatory disorders may not be triggered by the conventional progenitors of infection and injury, but rather caused by sustained tissue malfunction and persistent activation of endocrine and paracrine signaling, which ultimately block reestablishment of preinjury tissue function and systemic homeostasis.

Spinal cord injury (SCI) is a condition known to be characterized by extensive pro-inflammatory activity.[1] Acute inflammation occurs at the time of injury, but residual inflammation can persist beyond the initial insult indefinitely.[2] Chronic inflammation also results from common secondary complications of SCI (eg, pulmonary infections, urinary tract infections, and pressure ulcers).[1,3,4] Thus far, SCI research has primarily focused on modulating acute inflammation occurring within the spinal cord to decrease secondary damage

Corresponding author: Mark S. Nash, PhD, FACSM, Miller School of Medicine, University of Miami, 1095 NW 14th Terrace, R-48, Miami, FL 33136; e-mail: mnash@med.miami.edu

Top Spinal Cord Inj Rehabil 2017;23(3):207–217

www.thomasland.com

doi: 10.1310/sci2303-207

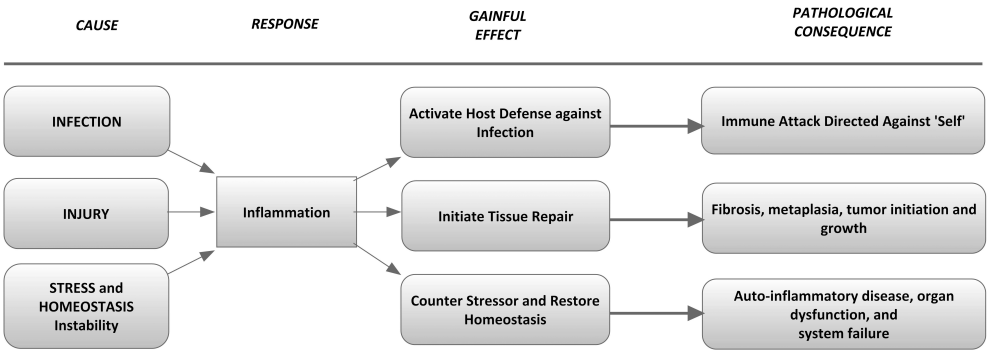

Figure 1. Cause, effect, and consequence of the inflammatory response.

and preserve sensorimotor function.[5,6] However, systemic inflammation impacts all body systems, not just one. As such, this monocular approach risks overlooking how chronic inflammation, by its very nature, may negatively impact the health of this population.

Evidence of heightened cardiometabolic disease risk after SCI[7,8] underscores an interest in post-SCI pro-inflammatory activity as both a biomarker and instigator of future tissue damage and dysfunction. Chronic low-grade inflammation is an established risk factor for metabolic disorders in persons without SCI.[9] Elevated values of C-reactive protein (CRP), a clinical marker of cardiovascular risk and systemic inflammation,[10,11] have repeatedly been demonstrated in persons with SCI.[8,12] These values correspond with high cardiovascular disease risk, per defined guidelines of the American Heart Association,[10,12] and are higher in persons with tetraplegia than paraplegia.[12] Although survival rates after SCI have greatly improved,[13] persons aging with SCI face an increased risk for secondary health complications such as cardiovascular disease.[14] Therefore, it is critical that effective treatments for *chronic* inflammation be developed to lessen the long-term medical risks that have been documented.[15,16]

We review the factors that contribute to a chronic inflammatory state after SCI. A recent review by Allison and Ditor described physiological mechanisms responsible for creating and sustaining immune dysfunction and chronic inflammation after SCI.[1] Our review builds on this work and considers both the gut microbiome and a pro-inflammatory phenotype as both cause and consequence of these risks.

Processes Contributing to Persistent Inflammatory Stress

Response to cord injury

Injury to the spinal cord produces an immediate inflammatory response occurring within hours of the initial insult[17,18] (**Figure 2**[19]). This neuroinflammation can be reparative or exacerbate the secondary injury, depending on the specific immune cells involved and the temporal response of those cells.[2,5,6,20,21] Suppression of acute inflammation is a legitimate clinical goal to preserve function after injury, but current treatment approaches have been unable to keep neuroinflammation from persisting through the chronic phase of injury.[2]

Autonomic dysfunction

SCI causes dysfunction of the autonomic nervous system[22] and immune system.[2] This interrelated dysfunction is expressed through pro-inflammation or immune suppression,[1,2,22,23] depending on which adrenergic receptor is stimulated by elevated catecholamines.[24] Additionally, physiological responses to bouts of autonomic dysfunction can initiate and exacerbate inflammatory stress,[25] creating an enabling environment for persistent non-resolving inflammation.[1]

It is accepted that autonomic dysreflexia triggered by bladder distension or bowel impaction/transit can result in a surge in catecholamines, crisis elevation in arterial blood pressure, reflexive bradycardia, and even myocardial or cerebral ischemia.[22,26,27] Sustained elevation

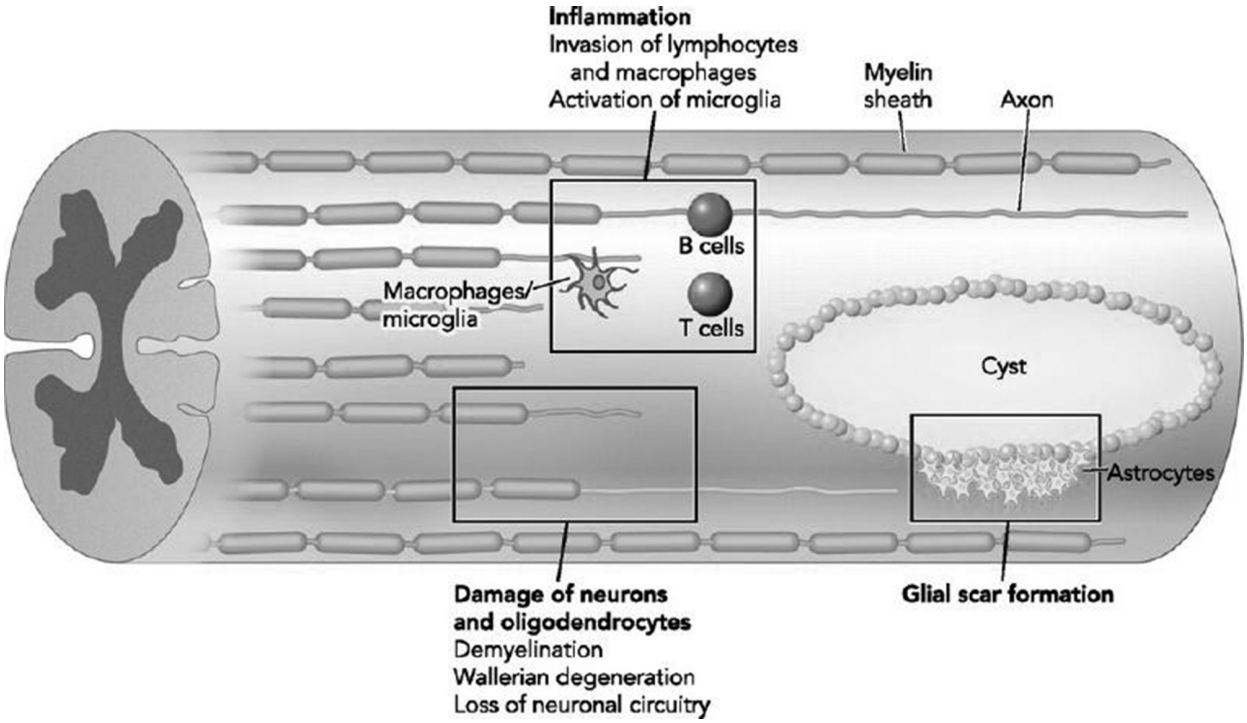

Figure 2. Immune response to acute spinal cord injury. Reproduced with permission from Obermair FJ, Schroter A, Thallmair M. Endogenous neural progenitor cells as therapeutic target after spinal cord injury. *Physiology (Bethesda)*. 2008;23:296-304. Copyright © 2008 American Physiological Society.

in catecholamines and blood pressure during these episodes leads to endothelial damage and inflammatory stress, accelerating pro-atherogenic processes and cardiovascular disease.[14,16,25] Although autonomic dysfunction and chronic inflammation likely contribute to the elevated risk for cardiometabolic disorders,[1,12,16,28] treatment of inflammation as a metabolic risk factor has not been implemented for this population.

Pain and depression

Pain and depression are common secondary complications of SCI.[15,29,30] It is estimated that more than 60% of persons with SCI experience chronic pain,[31] and 20% to 30% experience depression after injury.[32,33] Pain can be nociceptive or neuropathic in origin,[34] is related to depressive symptoms[35,36] and impaired sleep,[37,38] and may be provoked by the same noxious stimuli that triggers autonomic dysreflexia.[39] Research in persons without disability has demonstrated a strong relationship between inflammation and depression[40,41] and inflammation and pain,[42] suggesting that non-resolving inflammation may worsen these common secondary complications of SCI. A recent clinical trial found that targeting inflammation improved depression after SCI.[43] Considering the interrelated nature of inflammation with pain and depression[40-42] and the impact these conditions have on health and mortality risk after injury,[15,44] chronic inflammation may be a legitimate target in the all-inclusive management of SCI.

Acute infections

Acute infections of the lungs, urinary tract, and pressure ulcers are among the most common of secondary medical complications occurring after SCI,[1,3,4,45-47] represent the third highest source of all-cause mortality after injury,[45] and can even impact functional neurological recovery.[48]

Respiratory complications affect approximately 30% to 100% of persons with SCI, depending on the level of injury.[49-51] Pneumonia is one of the primary risk factors for increased mortality after

SCI[52] and is the primary cause of death for both the acute and chronic phases of SCI.[4,34,49] It is known that the presence of systemic inflammation worsens respiratory function and that, irrespective of the level or completeness of injury, higher levels of nonspecific acute phase reactant CRP and the inflammatory cytokine IL-6 are associated with reduced pulmonary function after SCI.[53]

The presence of symptomatic and asymptomatic bacteriuria poses risks for both acute and chronic inflammation. A recent study in persons with SCI reported that roughly 23% of participants had a symptomatic urinary tract infection,[45] although nearly 70% of participants had asymptomatic bacteriuria.[45] Asymptomatic bacteriuria has been associated with elevated inflammatory biomarkers in other populations[54] and thus may explain one source of non-resolving inflammation after SCI.

Pressure ulcers occur in 30% to 80% of persons with SCI.[47,55] If left untreated, pressure ulcers can lead to severe infection and bacteremia.[4] Pressure ulcers occur in parallel with secondary complications characterized by inflammation and may exacerbate conditions that lead to inflammation. In the former, for example, a higher prevalence of pressure ulcers has been observed in persons with pneumonia.[56] In the latter, changing of a bandage and debridement of pressure ulcers can trigger autonomic dysreflexia.[55] The concomitant occurrence of secondary conditions after SCI may impede the resolution of inflammation, as chronic inflammation can delay wound healing.[57] However, chronic inflammation may also expedite the development of additional complications. In acute SCI settings, elevated pro-inflammatory cytokines have been observed up to a week before the formation of the first pressure ulcer.[58] This occurrence may be an indication that the initial, mechanical insult has far-reaching, persistent effects.

Anatomical and lifestyle consequences of SCI contribute to the high prevalence of acute infections in this population. Prompt treatment and proper management of contributing factors (eg, effective bladder management[59] and pressure relieving strategies[60]) are several ways to decrease the incidence of acute infections and potentially reduce the impact of infection on mortality after SCI. However, treating other sources of inflammation (eg, pain, depression, autonomic dysreflexia, and bacteriuria) may be equally important. Persistent inflammation delays wound healing[57] and may increase the risk of developing secondary complications characterized by inflammation,[58] producing a vicious, self-perpetuating cycle.

Integumentary and skeletal injury

The integumentary system is a physical and immune barrier that protects the body from penetration by bacteria and other microorganisms. Breaching of this system by injury to the dermis and epidermis is an obvious source of acute infections in persons with SCI and may ultimately cause subdermal tissue infection. Pressure or shear forces can cause deep tissue injury; this injury produces an inflammatory response and, if left untreated, can progress into a pressure ulcer.[61-63] In a survey of wheelchair athletes, nearly 20% of participants reported blisters, lacerations, abrasions, and cuts as common injuries.[64] To our knowledge, the prevalence of these skin conditions in the general population of persons with SCI is unknown but would be expected to increase in the years post injury as skin loses collagen content and elasticity during the native course of aging-related immune senescence.

Up to 65% of persons with SCI experience at least one fracture, which is typically attributed to progressive bone loss occurring after injury.[65-68] This prevalence does not include occult fractures or microfractures that evade clinical detection. Acute fracture is characterized by inflammation[69,70] as the body initiates an inflammatory response to facilitate healing.[71] However, unresolved inflammation can impede bone repair.[72] Clinically, this may manifest in delayed fracture healing in persons who experience frequent urinary tract infections or in someone who incurs a subsequent wound due to altered mobility following a fracture. Osteoporosis is highly prevalent in other inflammatory conditions, such as chronic obstructive pulmonary disease.[73] Extrapolating, this suggests that elevated inflammation may increase the risk of SCI-induced osteoporosis.[74] In fact, elevated cytokines have been shown to increase the risk for fractures in nondisabled men.[75] Fractures have also been shown to increase

hospitalization time, increase the risk for pressure ulcers, and even increase mortality risk after SCI.[44,52,65,67,68]

Obesity and nutrition-mediated inflammation

It had been estimated that up to 66% of persons with SCI are overweight or obese.[76] A recent study involving 2 academic medical and rehabilitation centers reported that 83% of persons with SCI satisfied authoritative guidelines for classification as overweight/obese.[8] Obesity negatively influences health and quality of life after injury and has been related to increased rehospitalization rates,[77] severe pain,[77] and the development of pressure ulcers.[78,79]

A high-fat and hypercaloric intake,[16,80] combined with a decreased energy expenditure,[16,81] likely instigates the heightened prevalence of obesity in this population. In turn, obesity and a coincident high-fat diet may further exacerbate the chronic inflammatory state and metabolic risk after SCI.[82,83] While once thought of as a benign fat storage disorder, obesity is now recognized as a dynamic process in which fat contributes to immune and pro-inflammatory activity.[84] Not surprisingly, CRP is chronically elevated in persons with SCI[8,12] and is associated with waist circumference and metabolic syndrome.[11] In fact, as many as 76% of people with SCI demonstrate elevated CRP levels,[8] a predictive biomarker for metabolic syndrome.[11]

A recent recommendation suggested that obesity and elevated inflammation be considered as population-specific risk determinants for cardiometabolic syndrome after SCI.[8] To address these concerns, clinicians serving the SCI community must adopt proven interventions to treat obesity and cardiometabolic disease in this population, such as the recently adapted Diabetes Prevention Program.[83] Prioritizing this treatment for the aging SCI population is necessary because cardiometabolic syndrome has been shown to increase in prevalence as time after injury becomes prolonged.[85]

Exercise may be a therapeutic countermeasure to obesity and related inflammation after SCI. Exercise has been shown to reduce both inflammatory cytokines and fatigue in obese persons with type 2 diabetes.[86] In SCI, a recent behavioral intervention trial reported that promoting physical activity positively impacted both cardiometabolic outcomes and social participation after acute injury.[87] Exercise may decrease depression and pain as well as increase muscular strength and aerobic capacity after injury.[88,89] For these reasons, detailed exercise recommendations are available for persons with SCI.[88,90] Prescribing "exercise as medicine"[91,92] may be an effective way to address the inflammatory state and coincident secondary complications after SCI. Indeed, this approach has been suggested for other neurological conditions, such as stroke,[93,94] and is a significant component of recently described interventions for persons with SCI.[83]

Influence of bacteria and the microbiome

Recent research on the gut microbiome has uncovered a novel source of inflammation that may be especially relevant in addressing cardiometabolic risk.[95] The role of the gut microbiome in the development of metabolic syndrome has been described and involves several putative mechanisms, including bacterial-derived lipopolysaccharides (LPS) and short-chain fatty acids produced during fermentation of dietary polysaccharides.[95]

LPS found in the cell wall of Gram-negative bacteria is a highly inflammatory stimulant[96]; these bacterial wall components can induce "metabolic endotoxemia," a low-grade inflammatory state that can lead to metabolic syndrome.[95,97,98] Elevated LPS levels have been associated with obesity, insulin resistance, diabetes, and cardiovascular disease.[97,98] Typically, the gastrointestinal mucosal barrier restricts the passage of resident bacteria; however, breakdown of this barrier can lead to bacterial translocation.[99] Bacterial translocation has been shown to occur within 7 days after SCI in rodents.[100,101] If bacterial translocation also occurs and persists in humans, it could explain one source of the nonspecific inflammation commonly observed after injury.[1] It may also explain part of the elevated risk for cardiometabolic disorders in this population.[8,16] Furthermore, if the bacteria are predominantly of the Gram-negative type, LPS-associated gastrointestinal dysmotility[102] may explain one cause of gastrointestinal problems commonly observed after SCI.[103]

The second proposed factor linking the gut microbiome to metabolic syndrome involves short-chain fatty acids (SCFA), which are known to play an important role in regulating inflammation and insulin resistance.[104] SCFAs, including butyrate, are also involved in gut-brain signaling through the vagus nerve,[105] which has been implicated in regulating metabolic and immune homeostasis.[106] Additionally, SCFA levels have been negatively correlated with colonic transit time.[107]

Although an altered gut microbiome holds potential to impact health outcomes after SCI, this novel source of inflammation has only received limited attention in persons with SCI. To our knowledge, only one study has examined the gut microbiome in humans with SCI. In this study, a decrease in SCFA-producing bacteria was found in persons with differing levels of bowel dysfunction compared to controls.[108] An altered microbiome may explain additional secondary complications besides bowel dysfunction. One report described differences in the urinary microbiome between controls without SCI, subjects with SCI, and changes in the SCI urine microbiome with time since injury.[109] Because of the relationship between asymptomatic bacteriuria and elevated inflammatory biomarkers,[54] incorporating the microbiome in health assessment may provide critical evidence about contributors to chronic inflammation after SCI.

Additional research could identify whether putative changes in the gut microbiome after SCI contribute to metabolic risk in this population and examine whether manipulating the gut microbiome could alter the host's inflammatory,[96] metabolic,[95] gastrointestinal,[102] and even autonomic state[110] after SCI. Although LPS and SCFA levels may be modifiable by dietary interventions,[97,104] additional research is needed to understand which factors support sustained changes in microbiome composition. Manipulating this novel source of inflammation holds promise for persons with SCI as well as other conditions characterized by chronic inflammation.

Pro-inflammatory phenotype after SCI

As noted, recent attention has focused on blood levels of pro-inflammatory cytokines as a unified forerunner of cardiovascular disease[111,112] and a predictor of atherogenesis and cardiovascular events.[112] This pro-inflammatory phenotype has now been documented after SCI by several laboratories.[8,12,113-118] An expanding body of in vitro studies supports the view that inflammation may directly influence disease processes.[112] The pro-atherogenic activity of various serological products raises unique concerns for persons with SCI, as concentrations of blood-borne inflammatory cytokines are typically elevated. In most cases, testing of persons with SCI reveals pathologically elevated levels of CRP,[8,12] while elevated IL-6, soluble vascular adhesion molecule (sVCAM)-1, and endothelin-1 have also been reported.[118]

In addition to suspected elevation of vascular-derived CRP, chronic elevation of plasma-borne CRP and inflammatory cytokines (eg, IL-6) in persons with SCI can be attributed to various antecedents including overt clinical infection, background bacteriuria, excessive fat mass, and skin lesions[12,114,116] as well as the common sequelae of activity-induced musculoskeletal injury[119-121] and heterotopic ossification.[122] Noteworthy are the myriad sources for evolution of inflammatory products, the homogeneous signaling response despite unrelated origins and the finding that their levels after SCI surpass evidence-based cut-scores for elevated cardiovascular disease risk (eg, CRP >3 mg/dL), even without overt evidence of illness or inflammatory disease.[8,114,115,118,123]

Conclusions

The inflammatory response plays a significant role in both the acute and chronic phases of SCI as an interrelated, multifactorial process that adversely impacts health and quality of life after injury. In the acute phase, inflammation can lead to secondary damage, thus worsening the initial injury. Dysregulation in the autonomic nervous system can foster and produce inflammatory stress. Common secondary complications of SCI, such as acute infection, injury to the integumentary and skeletal systems, and obesity can all produce inflammation. They can also initiate and sustain chronic inflammation, leading to the exacerbation of existing conditions and creating a microenvironment suitable for the development and sustained risk of new medical complications.

Chronic inflammation amplifies the risk for cardiometabolic disorders after injury, although treating inflammation as an independent cardiometabolic risk factor has been widely overlooked for this population. Also, by exacerbating secondary complications, chronic inflammation directly impacts both the quality of life and mortality risk after injury. Research further implicates inflammation as cause for worsened pain and depression and even a hindrance of neurological recovery. Efforts to lessen the impact of secondary medical complications, such as pain, clearly align with the priorities of the SCI community.[124,125]

For these reasons, effectively managing chronic inflammation after SCI should be a high priority for clinicians and researchers who seek to improve the health and life quality of persons with SCI. It is imperative that chronic inflammation be routinely considered throughout the lifespan of the individual with SCI. Finally, future work is needed to examine whether changes in microbiome composition and the inflammatory phenotype can be manipulated after SCI and which interventions produce the most sustained and impactful changes in inflammation-mediated secondary complications.

Acknowledgments

We would like to thank April Mann for her assistance in technical review of the manuscript.

The authors report no conflicts of interest.

REFERENCES

1. Allison DJ, Ditor DS. Immune dysfunction and chronic inflammation following spinal cord injury. *Spinal Cord.* 2015;53(1):14-18.
2. Schwab JM, Zhang Y, Kopp MA, Brommer B, Popovich PG. The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Exp Neurol.* 2014;258:121-129.
3. McKinley WO, Gittler MS, Kirshblum SC, Stiens SA, Groah SL. Spinal cord injury medicine. 2. Medical complications after spinal cord injury: Identification and management. *Arch Phys Med Rehabil.* 2002;83(3 suppl 1):S58-64, S90-58.
4. Montgomerie JZ. Infections in patients with spinal cord injuries. *Clin Infect Dis.* 1997;25(6):1285-1290; quiz 1291-1282.
5. Gonzalez R, Glaser J, Liu MT, Lane TE, Keirstead HS. Reducing inflammation decreases secondary degeneration and functional deficit after spinal cord injury. *Exp Neurol.* 2003;184(1):456-463.
6. David S, Lopez-Vales R, Wee Yong V. Harmful and beneficial effects of inflammation after spinal cord injury: Potential therapeutic implications. *Handbook Clin Neurol.*2012;109:485-502.
7. Chopra AS, Miyatani M, Craven BC. Cardiovascular disease risk in individuals with chronic spinal cord injury: Prevalence of untreated risk factors and poor adherence to treatment guidelines. *J Spinal Cord Med.* 2016:1-8.
8. Nash MS, Tractenberg RE, Mendez AJ, et al. Cardiometabolic syndrome in people with spinal cord injury/disease: Guideline-derived and non-guideline risk components in a pooled sample. *Arch Phys Med Rehabil.* 2016;97(10):1696-1705.
9. Cooke AA, Connaughton RM, Lyons CL, McMorrow AM, Roche HM. Fatty acids and chronic low grade inflammation associated with obesity and the metabolic syndrome. *Eur J Pharmacol.* 2016;785:207-214.
10. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107(3):499-511.
11. Mirhafez SR, Ebrahimi M, Saberi Karimian M, et al. Serum high-sensitivity C-reactive protein as a biomarker in patients with metabolic syndrome: Evidence-based study with 7284 subjects. *Eur J Clin Nutr.* 2016;70(11):1298-1304.
12. Gibson AE, Buchholz AC, Martin Ginis KA. C-Reactive protein in adults with chronic spinal cord injury: Increased chronic inflammation in tetraplegia vs paraplegia. *Spinal Cord.* 2008;46(9):616-621.
13. Krause JS, Cao Y, DeVivo MJ, DiPiro ND. Risk and protective factors for cause-specific mortality after spinal cord injury. *Arch Phys Med Rehabil.* 2016;97(10):1669-1678.
14. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil..* 2007;86(2):142-152.
15. Cragg JJ, Noonan VK, Noreau L, Borisoff JF, Kramer JK. Neuropathic pain, depression, and cardiovascular disease: A national multicenter study. *Neuroepidemiology.* 2015;44(3):130-137.
16. Nash MS, Cowan RE, Kressler J. Evidence-based and heuristic approaches for customization of care in cardiometabolic syndrome after spinal cord injury. *J Spinal Cord Med.* 2012;35(5):278-292.
17. Dusart I, Schwab ME. Secondary cell death and the inflammatory reaction after dorsal hemisection of the rat spinal cord. *Eur J Neurosci.* 1994;6(5):712-724.

18. Beck KD, Nguyen HX, Galvan MD, Salazar DL, Woodruff TM, Anderson AJ. Quantitative analysis of cellular inflammation after traumatic spinal cord injury: Evidence for a multiphasic inflammatory response in the acute to chronic environment. *Brain.* 2010;133(Pt 2):433-447.
19. Obermair FJ, Schroter A, Thallmair M. Endogenous neural progenitor cells as therapeutic target after spinal cord injury. *Physiology (Bethesda).* 2008;23:296-304.21.
20. Bethea JR, Dietrich WD. Targeting the host inflammatory response in traumatic spinal cord injury. *Curr Opin Neurol.* 2002;15(3):355-360.
21. Donnelly DJ, Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. *Exp Neurol.* 2008;209(2):378-388.
22. Garstang SV, Miller-Smith SA. Autonomic nervous system dysfunction after spinal cord injury. *Phys Med Rehabil Clin N Am.* 2007;18(2):275-296, vi-vii.
23. Zhang Y, Guan Z, Reader B, et al. Autonomic dysreflexia causes chronic immune suppression after spinal cord injury. *J Neurosci.* 2013;33(32): 12970-12981.
24. Madden KS, Sanders VM, Felten DL. Catecholamine influences and sympathetic neural modulation of immune responsiveness. *Annu Rev Pharmacol Toxicol.* 1995;35:417-448.
25. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. *J Psychosom Res.* 2002;52(1):1-23.
26. Wan D, Krassioukov AV. Life-threatening outcomes associated with autonomic dysreflexia: A clinical review. *J Spinal Cord Med.* 2014;37(1):2-10.
27. Hou S, Rabchevsky AG. Autonomic consequences of spinal cord injury. *Compr Physiol.* 2014;4(4): 1419-1453.
28. Cowan RE, Nash MS. Cardiovascular disease, SCI and exercise: Unique risks and focused countermeasures. *Disabil Rehabil.* 2010;32(26):2228-2236.
29. Widerstrom-Noga E. Multidimensional clinical pain phenotypes after spinal cord injury. *Pain Manag.* 2012;2(5):467-478.
30. Ataoglu E, Tiftik T, Kara M, Tunc H, Ersoz M, Akkus S. Effects of chronic pain on quality of life and depression in patients with spinal cord injury. *Spinal Cord.* 2013;51(1):23-26.
31. Felix ER, Cruz-Almeida Y, Widerstrom-Noga EG. Chronic pain after spinal cord injury: what characteristics make some pains more disturbing than others? *J Rehabil Res Dev.* 2007;44(5):703-715.
32. Fann JR, Bombardier CH, Richards JS, Tate DG, Wilson CS, Temkin N. Depression after spinal cord injury: Comorbidities, mental health service use, and adequacy of treatment. *Arch Phys Med Rehabil.* 2011;92(3):352-360.
33. Williams R, Murray A. Prevalence of depression after spinal cord injury: A meta-analysis. *Arch Phys Med Rehabil.* 2015;96(1):133-140.
34. Sezer N, Akkus S, Ugurlu FG. Chronic complications of spinal cord injury. *World J Orthop.* 2015;6(1):24-33.
35. Wang JC, Chan RC, Tsai YA, et al. The influence of shoulder pain on functional limitation, perceived health, and depressive mood in patients with traumatic paraplegia. *J Spinal Cord Med.* 2015;38(5): 587-592.
36. Cruz-Almeida Y, Felix ER, Martinez-Arizala A, Widerstrom-Noga EG. Pain symptom profiles in persons with spinal cord injury. *Pain Med (Malden, Mass.).* 2009;10(7):1246-1259.
37. Avluk OC, Gurcay E, Gurcay AG, Karaahmet OZ, Tamkan U, Cakci A. Effects of chronic pain on function, depression, and sleep among patients with traumatic spinal cord injury. *Ann Saudi Med.* 2014;34(3):211-216.
38. Widerstrom-Noga EG, Felipe-Cuervo E, Yezierski RP. Chronic pain after spinal injury: interference with sleep and daily activities. *Arch Phys Med Rehabil.* 2001;82(11):1571-1577.
39. Widerstrom-Noga E, Cruz-Almeida Y, Krassioukov A. Is there a relationship between chronic pain and autonomic dysreflexia in persons with cervical spinal cord injury? *J Neurotrauma.* 2004;21(2):195-204.
40. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci.* 2008;9(1):46-56.
41. Fischer CW, Elfving B, Lund S, Wegener G. Behavioral and systemic consequences of long-term inflammatory challenge. *J Neuroimmunol.* 2015;288:40-46.
42. White FA, Bhangoo SK, Miller RJ. Chemokines: Integrators of pain and inflammation. *Nat Rev Drug Discov.* 2005;4(10):834-844.
43. Allison DJ, Ditor DS. Targeting inflammation to influence mood following spinal cord injury: A randomized clinical trial. *J Neuroinflammation.* 2015;12:204.
44. Krause JS, Carter RE, Pickelsimer EE, Wilson D. A prospective study of health and risk of mortality after spinal cord injury. *Arch Phys Med Rehabil.* 2008;89(8):1482-1491.
45. Togan T, Azap OK, Durukan E, Arslan H. The prevalence, etiologic agents and risk factors for urinary tract infection among spinal cord injury patients. *Jundishapur J Microbiol.* 2014;7(1):e8905.
46. Grossman RG, Frankowski RF, Burau KD, et al. Incidence and severity of acute complications after spinal cord injury. *J Neurosurg Spine.* 2012;17(suppl 1):119-128.
47. Saunders LL, Krause JS, Acuna J. Association of race, socioeconomic status, and health care access with pressure ulcers after spinal cord injury. *Arch Phys Med Rehabil.* 2012;93(6):972-977.
48. Failli V, Kopp MA, Gericke C, et al. Functional neurological recovery after spinal cord injury is impaired in patients with infections. *Brain.* 2012;135(Pt 11):3238-3250.
49. Galeiras Vazquez R, Rascado Sedes P, Mourelo Farina M, Montoto Marques A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. *BioMed Res Int.* 2013;2013:168757.

50. Winslow C, Rozovsky J. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil.* 2003;82(10):803-814.
51. Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehabil.* 1994;75(3):270-275.
52. Cao Y, Krause JS, DiPiro N. Risk factors for mortality after spinal cord injury in the USA. *Spinal Cord.* 2013;51(5):413-418.
53. Garshick E, Stolzmann KL, Gagnon DR, Morse LR, Brown R. Systemic inflammation and reduced pulmonary function in chronic spinal cord injury. *PM R.* 2011;3(5):433-439.
54. Prio TK, Bruunsgaard H, Roge B, Pedersen BK. Asymptomatic bacteriuria in elderly humans is associated with increased levels of circulating TNF receptors and elevated numbers of neutrophils. *Exp Gerontol.* 2002;37(5):693-699.
55. Parikh RP, Matthew Franzen M, Cecille Pope C, Lisa Gould L. Autonomic dysreflexia: Be aware and be prepared. *Wounds.* 2012;24(6):160-167.
56. Krishnan S, Karg PE, Boninger ML, Brienza DM. Association between presence of pneumonia and pressure ulcer formation following traumatic spinal cord injury. *J Spinal Cord Med.* 2016:1-8.
57. Yuan R, Geng S, Chen K, Diao N, Chu HW, Li L. Low-grade inflammatory polarization of monocytes impairs wound healing. *J Pathol.* 2016;238(4): 571-583.
58. Krishnan S, Karg PE, Boninger ML, et al. Early detection of pressure ulcer development following traumatic spinal cord injury using inflammatory mediators. *Arch Phys Med Rehabil.* 2016;97(10:1656-1662.
59. Singh R, Rohilla RK, Sangwan K, Siwach R, Magu NK, Sangwan SS. Bladder management methods and urological complications in spinal cord injury patients. *Indian J Orthop.* 2011;45(2):141-147.
60. Baron J, Swaine J, Presseau J, et al. Self-management interventions to improve skin care for pressure ulcer prevention in people with spinal cord injuries: A systematic review protocol. *Syst Rev.* 2016;5(1):150.
61. Aoi N, Yoshimura K, Kadono T, et al. Ultrasound assessment of deep tissue injury in pressure ulcers: Possible prediction of pressure ulcer progression. *Plast Reconstr Surg.* 2009;124(2):540-550.
62. Berlowitz DR, Brienza DM. Are all pressure ulcers the result of deep tissue injury? A review of the literature. *Ostomy/wound Manag.* 2007;53(10):34-38.
63. Gefen A, Farid KJ, Shaywitz I. A review of deep tissue injury development, detection, and prevention: Shear savvy. *Ostomy/wound Manag.* 2013;59(2):26-35.
64. Curtis KA, Dillon DA. Survey of wheelchair athletic injuries: Common patterns and prevention. *Paraplegia.* 1985;23(3):170-175.
65. Edwards WB, Schnitzer TJ. Bone imaging and fracture risk after spinal cord injury. *Curr Osteoporos Rep.* 2015;13(5):310-317.
66. Bauman WA, Cardozo CP. Osteoporosis in individuals with spinal cord injury. *PM R.* 2015;7(2):188-201; quiz 201.
67. Hammond ER, Metcalf HM, McDonald JW, Sadowsky CL. Bone mass in individuals with chronic spinal cord injury: Associations with activity-based therapy, neurologic and functional status, a retrospective study. *Arch Phys Med Rehabil.* 2014;95(12): 2342-2349.
68. Frotzler A, Cheikh-Sarraf B, Pourtehrani M, Krebs J, Lippuner K. Long-bone fractures in persons with spinal cord injury. *Spinal Cord.* 2015;53(9): 701-704.
69. Li H, Liu J, Yao J, Zhong J, Guo L, Sun T. Fracture initiates systemic inflammatory response syndrome through recruiting polymorphonuclear leucocytes. *Immunol Res.* 2016;64(4):1053-1059.
70. Hauser CJ, Zhou X, Joshi P, et al. The immune microenvironment of human fracture/soft-tissue hematomas and its relationship to systemic immunity. *J Trauma.* 1997;42(5):895-903; discussion 903-894.
71. Hoff P, Gaber T, Strehl C, et al. Immunological characterization of the early human fracture hematoma. *Immunol Res.* 2016.
72. Loi F, Cordova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone.* 2016;86:119-130.
73. Okazaki R, Watanabe R, Inoue D. Osteoporosis associated with chronic obstructive pulmonary disease. *J Bone Metab.* 2016;23(3):111-120.
74. Troy KL, Morse LR. Measurement of bone: Diagnosis of SCI-induced osteoporosis and fracture risk prediction. *Top Spinal Cord Injury Rehabil.* 2015;21(4): 267-274.
75. Cauley JA, Barbour KE, Harrison SL, et al. Inflammatory markers and the risk of hip and vertebral fractures in men: The osteoporotic fractures in men (MrOS). *J Bone Miner Res.* 2016;31(12):2129-2138
76. Rajan S, McNeely MJ, Warms C, Goldstein B. Clinical assessment and management of obesity in individuals with spinal cord injury: A review. *J Spinal Cord Med.* 2008;31(4):361-372.
77. Chen Y, Cao Y, Allen V, Richards JS. Weight matters: Physical and psychosocial well being of persons with spinal cord injury in relation to body mass index. *Arch Phys Med Rehabil.* 2011;92(3):391-398.
78. Li C, DiPiro ND, Cao Y, Szlachcic Y, Krause J. The association between metabolic syndrome and pressure ulcers among individuals living with spinal cord injury. *Spinal Cord.* 2016;54(11):967-972.
79. Elsner JJ, Gefen A. Is obesity a risk factor for deep tissue injury in patients with spinal cord injury? *J Biomech.* 2008;41(16):3322-3331.
80. Levine AM, Nash MS, Green BA, Shea JD, Aronica MJ. An examination of dietary intakes and nutritional status of chronic healthy spinal cord injured individuals. *Paraplegia.* 1992;30(12):880-889.
81. Buchholz AC, Pencharz PB. Energy expenditure in chronic spinal cord injury. *Curr Opin Clin Nutr Metab Care.* 2004;7(6):635-639.
82. De Lorenzo A, Bernardini S, Gualtieri P, et al. Mediterranean meal versus Western meal effects on postprandial ox-LDL, oxidative and inflammatory gene expression in healthy subjects: A randomized controlled trial for nutrigenomic approach in cardiometabolic risk [published online ahead of print October 5, 2016]. *Acta Diabetol.*

83. Nash MS, Kressler J. Model programs to address obesity and cardiometabolic disease: Interventions for suboptimal nutrition and sedentary lifestyles. *Arch Phys Med Rehabil.* 2016;97(9 suppl):S238-S246.
84. Mancuso P. The role of adipokines in chronic inflammation. *Immunotargets Ther.* 2016;5:47-56.
85. Szlachcic Y, Adkins RH, Govindarajan S, Cao Y, Krause JS. Cardiometabolic changes and disparities among persons with spinal cord injury: A 17-year cohort study. *Top Spinal Cord Inj Rehabil.* 2014;20(2):96-104.
86. Abd El-Kader SM, Al-Jiffri OH, Al-Shreef FM. Aerobic exercises alleviate symptoms of fatigue related to inflammatory cytokines in obese patients with type 2 diabetes. *Afr Health Sci.* 2015;15(4):1142-1148.
87. Nooijen CF, Stam HJ, Sluis T, Valent L, Twisk J, van den Berg-Emons RJ. A behavioral intervention promoting physical activity in people with subacute spinal cord injury: Secondary effects on health, social participation and quality of life [published online ahead of print July 4, 2016]. *Clin Rehabil.*
88. Tweedy SM, Beckman EM, Geraghty TJ, et al. Exercise and sports science Australia (ESSA) position statement on exercise and spinal cord injury [published online ahead of print October 31, 2016]. *J Sci Med Sport.*
89. DiPiro ND, Embry AE, Fritz SL, Middleton A, Krause JS, Gregory CM. Effects of aerobic exercise training on fitness and walking-related outcomes in ambulatory individuals with chronic incomplete spinal cord injury. *Spinal Cord.* 2016;54(9): 675-681.
90. Jacobs PL, Nash MS. Exercise recommendations for individuals with spinal cord injury. *Sports Med (Auckland).* 2004;34(11):727-751.
91. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports.* 2015;25(suppl 3):1-72.
92. Cowan R, Malone L, Nash M. Exercise is Medicine™: Exercise prescription after SCI to manage cardiovascular disease risk factors. *Top Spinal Cord Inj Rehabil.* 2009;14(3):69-83.
93. Coelho Junior HJ, Gambassi BB, Diniz TA, et al. Inflammatory mechanisms associated with skeletal muscle sequelae after stroke: Role of physical exercise. *Mediators Inflamm.* 2016;2016:3957958.
94. Ploughman M, Kelly LP. Four birds with one stone? Reparative, neuroplastic, cardiorespiratory, and metabolic benefits of aerobic exercise poststroke. *Curr Opin Neurol.* 2016;29(6):684-692.
95. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. *World J Gastroenterol.* 2014;20(43):16079-16094.
96. Carvalho BM, Saad MJ. Influence of gut microbiota on subclinical inflammation and insulin resistance. *Mediators Inflamm.* 2013;2013:986734.
97. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007;56(7):1761-1772.
98. Neves AL, Coelho J, Couto L, Leite-Moreira A, Roncon-Albuquerque R. Metabolic endotoxemia: A molecular link between obesity and cardiovascular risk. *J Molec Endocrinol.* 2013;51(2):R51-R64.
99. MacFie J. Current status of bacterial translocation as a cause of surgical sepsis. *Br Med Bull.* 2004;71:1-11.
100. Liu J, An H, Jiang D, et al. Study of bacterial translocation from gut after paraplegia caused by spinal cord injury in rats. *Spine.* 2004;29(2):164-169.
101. Kigerl KA, Hall JC, Wang L, Mo X, Yu Z, Popovich PG. Gut dysbiosis impairs recovery after spinal cord injury. *J Exp Med.* 2016;213(12):2603-2620.
102. De Winter BY, De Man JG. Interplay between inflammation, immune system and neuronal pathways: Effect on gastrointestinal motility. *World J Gastroenterol.* 2010;16(44):5523-5535.
103. Williams RE, 3rd, Bauman WA, Spungen AM, et al. SmartPill technology provides safe and effective assessment of gastrointestinal function in persons with spinal cord injury. *Spinal Cord.* 2012;50(1):81-84.
104. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Evidence for the gut microbiota short-chain fatty acids as key pathophysiological molecules improving diabetes. *Mediators Inflamm.* 2014;2014:162021.
105. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. *Adv Exp Med Biol.* 2014;817:115-133.
106.Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex—linking immunity and metabolism. *Nat Rev Endocrinol.* 2012;8(12):743-754.
107. Ringel-Kulka T, Choi CH, Temas D, et al. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. *Am J Gastroenterol.* 2015;110(9):1339-1346.
108. Gungor B, Adiguzel E, Gursel I, Yilmaz B, Gursel M. Intestinal microbiota in patients with spinal cord injury. *PloS one.* 2016;11(1):e0145878.
109. Fouts DE, Pieper R, Szpakowski S, et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. *J Trans Med.* 2012;10:174.
110. Tanida M, Yamano T, Maeda K, Okumura N, Fukushima Y, Nagai K. Effects of intraduodenal injection of Lactobacillus johnsonii La1 on renal sympathetic nerve activity and blood pressure in urethane-anesthetized rats. *Neurosci Lett.* 2005;389(2):109-114.
111. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). *Ann Rev Immunol.* 2009;27:165-197.
112. Hansson GK, Libby P. The immune response in atherosclerosis: A double-edged sword. *Nat Rev Immunol.* 2006;6(7):508-519.
113. Davies AL, Hayes KC, Dekaban GA. Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Arch Phys Med Rehabil.* 2007;88(11):1384-1393.
114. Frost F, Roach MJ, Kushner I, Schreiber P. Inflammatory C-reactive protein and cytokine levels in asymptomatic people with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2005;86(2):312-317.

115. 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(1):36-41.
116. Manns PJ, McCubbin JA, Williams DP. Fitness, inflammation, and the metabolic syndrome in men with paraplegia. *Arch Phys Med Rehabil.* 2005;86(6):1176-1181.
117. Morse LR, Stolzmann K, Nguyen HP, et al. Association between mobility mode and C-reactive protein levels in men with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2008;89(4):726-731.
118. Wang TD, Wang YH, Huang TS, Su TC, Pan SL, Chen SY. Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury. *J Formos Med Assoc.* 2007;106(11):919-928.
119. Carp SJ, Barr AE, Barbe MF. Serum biomarkers as signals for risk and severity of work-related musculoskeletal injury. *Biomark Med.* 2008;2(1): 67-79.
120. Matute Wilander A, Karedal M, Axmon A, Nordander C. Inflammatory biomarkers in serum in subjects with and without work related neck/shoulder complaints. *BMC Musculoskelet Disord.* 2014;15:103.
121. Pritchett JW. C-reactive protein levels determine the severity of soft-tissue injuries. *Am J Orthop (Belle Mead, NJ).* 1996;25(11):759-761.
122. Estrores IM, Harrington A, Banovac K. C-reactive protein and erythrocyte sedimentation rate in patients with heterotopic ossification after spinal cord injury. *J Spinal Cord Med.* 2004;27(5):434-437.
123. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am College Cardiol.* 2010;56(25):e50-103.
124. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma.* 2004;21(10):1371-1383.
125. Lo C, Tran Y, Anderson K, Craig A, Middleton J. Functional priorities in persons with spinal cord injury: Using discrete choice experiments to determine preferences. *J Neurotrauma.* 2016;33(21): 1958-1968.