
Inflammatory Stress Effects on Health and Function After Spinal Cord Injury

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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

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Top Spinal Cord Inj Rehabil 2017;23(3):207–217
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www.thomasland.com

doi: 10.1310/sci2303-207

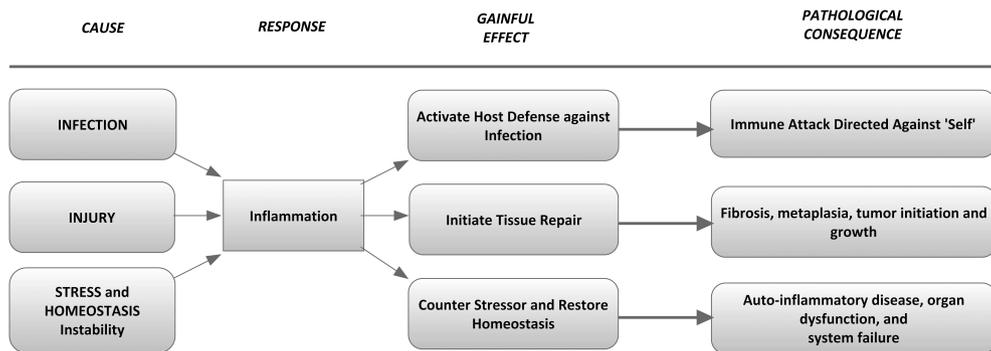


Figure 1. Cause, effect, and consequence of the inflammatory response.

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 system²² 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

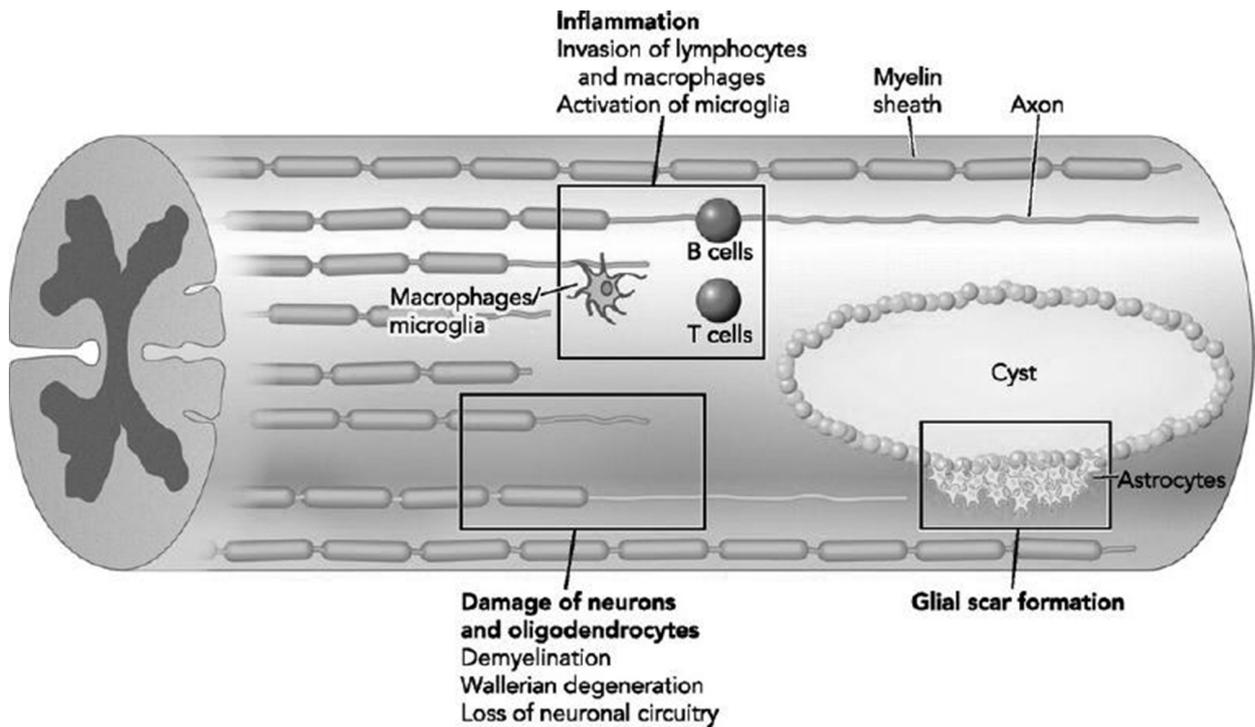


Figure 2. Immune response to acute spinal cord injury. Reproduced with permission from Obermair FJ, Schroter A, Thallmair M. Endogenous neural progenitor cells as therapeutic target after spinal cord injury. *Physiology (Bethesda)*. 2008;23:296-304. Copyright © 2008 American Physiological Society.

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 depression⁴⁰⁻⁴² 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

SCI⁵² 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 populations⁵⁴ 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 management⁵⁹ and pressure relieving strategies⁶⁰) 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 healing⁵⁷ 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 stimulant⁹⁶; 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 dysmotility¹⁰² 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 state¹¹⁰ 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 injury¹¹⁹⁻¹²¹ 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.

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