

Center of Excellence on the Medical Consequences of Spinal Cord Injury

The mission the VA Rehabilitation, Research & Development Center of Excellence for the Medical Consequences of Spinal Cord Injury is to improve the quality of life, health and well-being, and increase longevity by identifying, intervening, and/or preventing the secondary medical consequences that result from having a spinal cord injury.

The Center of Excellence for the Medical Consequences of Spinal Cord Injury has made many important contributions toward characterizing, understanding and treating the secondary medical as a result of spinal cord injury, a devastating neurological disorder that effects 50,000 veterans. This work has contributed to the characterization and potential treatment of diverse medical complications of spinal cord injury (SCI) that include impairments in carbohydrate and lipid metabolism, bowel dysfunction, alterations in body composition, depression of the hypothalamic/pituitary axis, osteoporosis, pulmonary dysfunction, abnormalities of autonomic and cardiovascular function, and pressure ulcers. Investigators from this Center have published over 100 papers in the field of SCI research.

Endocrine Program:

The Center has been a leader in demonstrating that persons with SCI are predisposed to **impaired metabolism of carbohydrates and lipids**. The investigators first to described the high prevalence of diabetes, insulin resistance, and adverse changes in lipid profiles: 1 in 5 patients with SCI have frank diabetes and 3 in 5 have carbohydrate abnormalities,. Diabetes and insulin resistance increase risk for heart disease, and also has an adverse impact on quality of life, as well as having the potential to be a notable cost burden to the VA healthcare system. These finding have been confirmed in several VA and nonVA large SCI population studies. As a result of these findings, SCI Services across the country have begun oral glucose tolerance testing and complete lipid panels as part of their annual physical examinations. To permit early diagnosis and intervention/treatment, which is vital to reduce complications.

Investigators from the Center have identified depression of the **hypothalamic/pituitary axis** in persons with SCI. Levels of testosterone and growth hormone/insulin-like growth factor 1 (IGF-1) are reduced to below normal values. Persons with SCI who were prescribed baclofen for muscle spasticity had the return of IGF-1 levels to normal, as well as those administered low-dose baclofen in a prospective manner, an important clinical finding with important implications for the preservation of lean tissue mass, muscle function, and independence. A testosterone replacement trial is underway to determine if hormone replacement therapy is beneficial in persons with chronic injury.

Disuse **osteoporosis** is a common problem, predisposing those with SCI to long-bone fractures. Approximately one-third of persons with SCI have been shown to have absolutely **low vitamin D levels, with the majority of the population having relatively low levels**. Work has begun to determine the optimum vitamin D replacement dose and the effect in those with vitamin D

deficiency of temporarily raising the serum calcium level with a calcium infusion on bone resorption/turnover. Two studies have tested whether other pharmacological interventions mitigate bone loss in acute and chronic SCI: the use of intravenous pamidronate, a bisphosphonate, to prevent bone loss after acute SCI, and the use of a vitamin D analog, 1-alpha vitamin D₂, in those with chronic SCI. These studies found a small beneficial effect on bone loss. Perhaps, more importantly, this work highlights the need for more efficacious therapies to prevent or reverse bone loss associated with immobilization.

Pulmonary Program:

Investigators in the research Center were the first to describe an **asthma-like condition in individuals with cervical SCI**, probably the result of disruption of the sympathetic innervation to the lungs. The pulmonary complications associated with altered sympathetic neural influences to the lung include airway hyperreactivity to exogenous stimuli, increased airway resistance, and an increased prevalence of respiratory symptoms. Interventional studies are underway, and preliminary observations have shown that tonic bronchoconstriction is completely reversible with inhalation of ipratropium bromide, a cholinergic agonist, while the response to an inhaled adrenergic agent, albuterol, was somewhat less efficacious. In addition, because of paralysis of muscles of respiration, a restrictive component of breathing has been more fully characterized, with an effort to increase the strength of the muscles of respiration and cough.

Gastroenterology Program:

Work performed by the Center has addressed **bowel dysfunction**, with a concerted effort to increase bowel motility. The investigators have demonstrated rapid and complete bowel evacuation by the administration of intravenous or intramuscular administration of neostigmine, a cholinergic agent, combined with glycopyrrolate, an anti-cholinergic agent on the cardiopulmonary system, but not on the bowel. Preliminary data have indicated that subcutaneous administration of these agents is also effective, suggesting that this modality could be employed by outpatients as part of their routine bowel care regimens. There is the potential for alternative routes of administration to facilitate application of this combination of drugs on an outpatient basis. This form of combination pharmacological therapy, if future studies confirm that it is well tolerated and efficacious, will undoubtedly lead to a major advance in bowel care and, thus, quality of life. This work has led to a provisional patent through the Office of Technology Transfer within the Department of Veterans Affairs.

Cardiovascular/Autonomic Program:

Investigators from the Center have reported a blunted sympathetic response to up-right postures in persons with paraplegia below T₆ (persons with intact cardiac sympathetic innervation), and the increase in heart rate was predominantly due to vagal withdrawal. Additional preliminary studies have suggested that there is an up-regulation of vascular production of nitric oxide, a very

potent endogenous vasodilator, which may contribute to refractory orthostatic hypotension in persons with tetraplegia. As many as one-third of veterans with tetraplegia experience **refractory orthostatic hypotension**. The potential for treatment of these persons has been suggested by the findings that an inhibitor of nitric oxide synthesis raises blood pressure in persons with tetraplegia.

Molecular Program:

The molecular program aims to: define the molecular mechanisms by which anabolic agents block muscle loss and promote muscle gain; characterize the molecular basis for easy fatigue of muscle during functional electrical stimulation; and explore the potential for anabolic steroids to improve functional recovery after SCI. Through such knowledge, novel and more effective treatments can be developed to improve function after SCI. Several projects examining molecular mechanisms of anabolic steroid action are now ongoing. The first of these is determining the molecular mechanisms by which testosterone blocks glucocorticoid-induced muscle atrophy through analysis of genome-wide effects of dexamethasone alone or in combination with testosterone on gene expression in skeletal muscle. Our current work extends findings from the microarray studies which suggest important effects of testosterone to normalize glucocorticoid-induced alterations in regulatory pathways controlling rates of protein synthesis, as well as expression of specific transcription factors and transcriptional co-activators linked to muscle atrophy. We have recently observed that anabolic steroids reduce denervation atrophy and expression of muscle ubiquitin ligases linked to muscle atrophy during the subacute phase while having no effect acutely. DNA microarray analysis reveals clear differences in effects of anabolic steroids on gene expression profiles between acute and subacute denervation, which are likely to provide insights into both mechanisms of anabolic steroid action, as well as barriers blocking anabolic steroid actions on muscle. We are currently analyzing and confirming these microarray findings. To characterize the molecular basis for limitations in muscle responses to exercise by functional electrical stimulation, we are currently performing a microarray analysis comparing changes in gene expression caused by exercise in normal and spinal cord injured rats to determine how the biologic response of muscle to exercise is different in individuals with SCI. Finally, we are examining the possibility that an anabolic steroid will improve functional recovery after SCI in animal models.

Cooperative Study #535 Pressure Ulcer Study:

Persons with spinal cord injury (SCI) are at increased risk of developing a Stage III or IV (full-thickness) pressure ulcer. These wounds exact a tremendous personal and financial cost. An intervention that proves efficacious in healing this chronic medical condition would be of enormous medical, social, and economic benefit. From preliminary studies, it appears that there is a role for anabolic steroid agents as a systemic approach in the care of patients with pressure ulcers. This class of medications has been demonstrated to be efficacious in healing of burns by reducing catabolism. Oxandrolone is a potent anabolic steroid agent with few side effects, is FDA approved to restore body weight, and has been reported to heal refractory pressure ulcers in persons with SCI.

The primary objective is to determine whether SCI inpatients with a chronic Stage III or IV pressure ulcer of the pelvic region who are randomized to receive 24 weeks of optimized clinical care (i.e., guideline-driven care with nutritional support) and an oral anabolic steroid agent (oxandrolone) will have a greater percent of healed pressure ulcers than those who receive placebo and the same standards of clinical care. The major secondary objective is to determine whether the healed pressure ulcer will remain closed for 8 weeks.

This is a five-year prospective, randomized, double blind, placebo-controlled clinical trial. Patients with chronic SCI who have a difficult-to-heal pressure ulcer of the pelvic region and meet all inclusion/exclusion criteria will be randomized to either the anabolic agent or placebo treatment. Pressure ulcer size (area measurement) and characteristics will be measured by a commercial digital imaging technology with a computer software database component.

Lokomat Program:

Lokomat therapy on a treadmill is an established intervention for improving over-ground walking function in various neurological conditions, including traumatic brain injury, spinal cord injury, multiple sclerosis, and stroke, but it is not limited to these populations. Through intensive training sessions, patients begin the process of re-learning to walk upright until partial, or even in some cases, complete functional mobility is restored.

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