Cardiometabolic Disease after Spinal Cord Injuries: At the Crossroads of Lifestyle and Molecular Management Strategies

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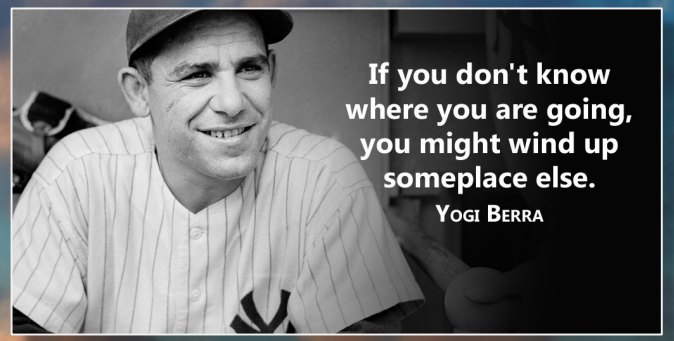
Disclosures

- The Guideline Panel on *Cardiometabolic Disease Identification and Management* was supported by the Paralyzed Veterans of America as part of the Consortium for Spinal Cord Medicine.* Comments about this guideline represent opinions of the PVA. Is there a Consumer Guide?
- The presenter is an Executive Board member of the American Spinal Injury Association, but his opinions don't necessarily reflect those of ASIA.
- Some of the things said in this talk may not have been said at all, or, not said in the way that they were said. Opinions about forks, Mark Twain, roads, and baseball are the presenter's alone.
- No other conflicts or financial alliances are declared.

- https://pva-cdnendpoint.azureedge.net/prod/libraries/media/pva/library/publications/cpg_cardiometabolic-risk_digital.pdf
- Nash MS, Groah SL, Gater DR, Dyson-Hudson TA, Lieberman JA, Myers J, Sabharwal S, Taylor AJ. Identification and management of cardiometabolic risk after spinal cord injury. The Journal of Spinal Cord Medicine. 2019 Sep 3;42(5):643-77.

“When you come to the fork in the road, take it.”
Lawrence Berra



A new and brighter day.

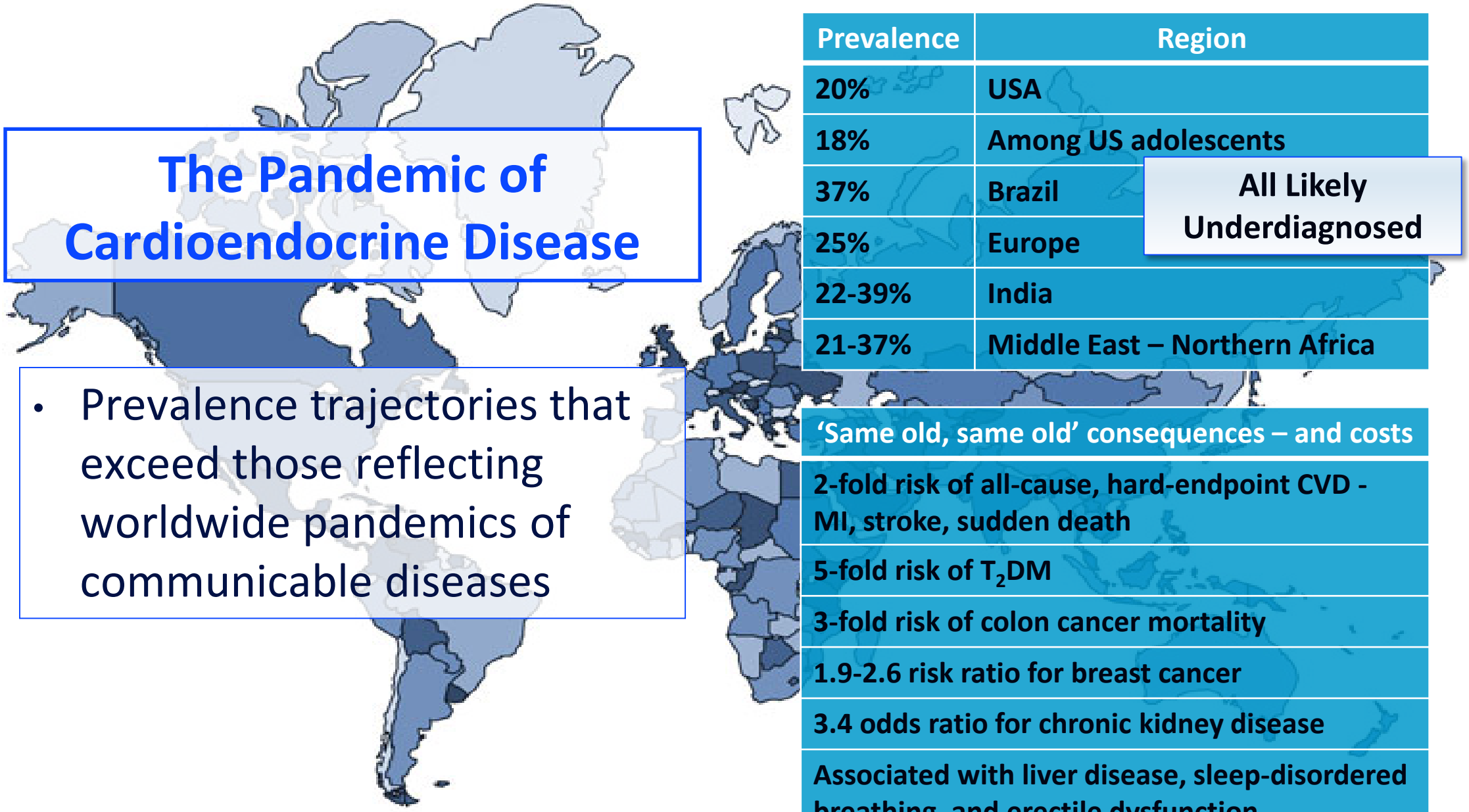
Same old, same old.

To be discussed…

Data supporting an urgency to act and a plan for action

The Pandemic of Cardioendocrine Disease

- Prevalence trajectories that exceed those reflecting worldwide pandemics of communicable diseases



Prevalence	Region
20%	USA
18%	Among US adolescents
37%	Brazil
25%	Europe
22-39%	India
21-37%	Middle East – Northern Africa

All Likely Underdiagnosed

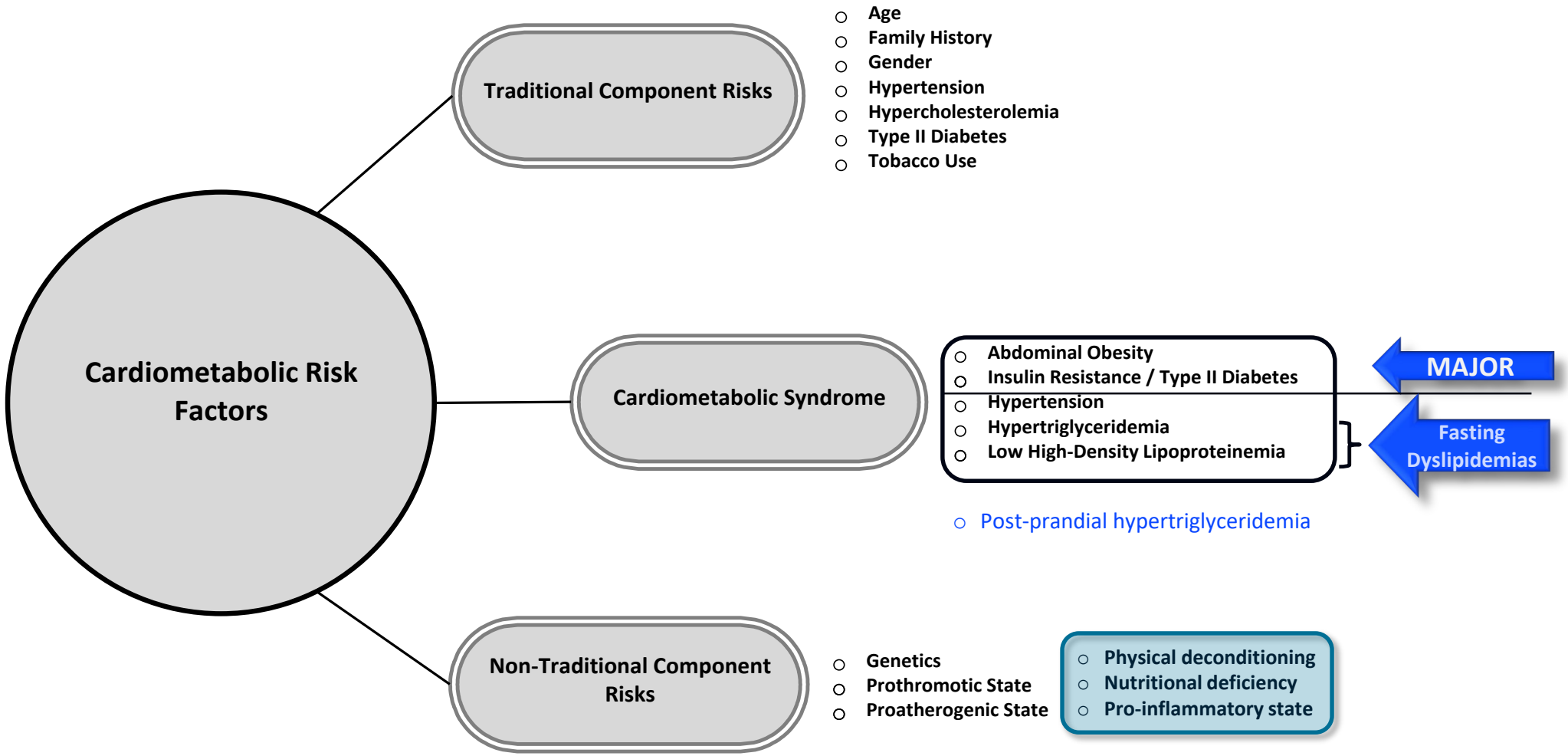
‘Same old, same old’ consequences – and costs
2-fold risk of all-cause, hard-endpoint CVD - MI, stroke, sudden death
5-fold risk of T_2DM
3-fold risk of colon cancer mortality
1.9-2.6 risk ratio for breast cancer
3.4 odds ratio for chronic kidney disease
Associated with liver disease, sleep-disordered breathing, and erectile dysfunction

Grundy 2005

World Report on Disability
http://www.gpdd-online.org

- More than one billion people in the world live with some form of disability…
- Prevalence is on the rise…
- Aging and chronic disease is a special problem…
- Diabetes and cardiovascular disease are among the most concerning of conditions noted in the ’Report’…

A pro-thrombotic and pro-inflammatory metabolic disorder characterized by coalescing of five risk factors that hasten all-cause atherogenic disease…



Components Risks of the Cardiometabolic Syndrome: AHA Guidelines Designate Any 3 of the Following:

SCI

Low HDL
50-60%

Obesity/ Overweight

30-70%

Insulin Resistance – Diabetes

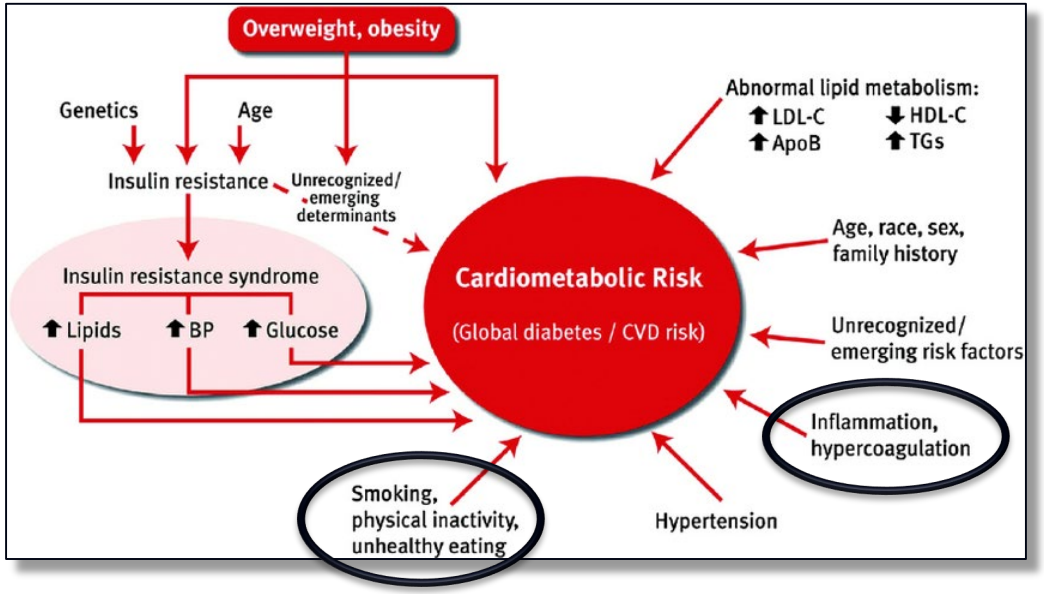
20-36%

Risk Factor	Defining Level
Abdominal Obesity	Waist Circumference • >102 cm (>40 in) ♂ • > 88 cm (>35 in) ♀
Fasting Triglycerides	• ≥ 150 mg/dL
Fasting High-density Lipoprotein Cholesterol	• < 40 mg/dL ♂ • < 50 mg/dL ♀
[Pre]Hypertension	• ≥ 130 / ≥ 85
Insulin Resistance/ Impaired Fasting Glucose	• ≥ 110 mg/dL World Health Organization; ≥100 mg/dL

Nash, M.S. and JL Bilzon. Guideline Approaches for Cardioendocrine Disease Surveillance and Treatment Following Spinal Cord Injury. *In*: Sadowsky C. (Ed.) Spinal Cord Injury Rehabilitation, Current Physical Medicine and Rehabilitation Reports; DOI: 10.1007/s40141-018-0203-z2018.

The Cardiometabolic Syndrome as a ‘Syndrome’

- Multiple interrelated risk factors constitute a ‘syndrome’.
- Multiple independent risk factors are known to worsen disease prognosis.
- **Credible evidence now indicates that any single major risk factor almost imposes the same risks as the “Syndrome”**

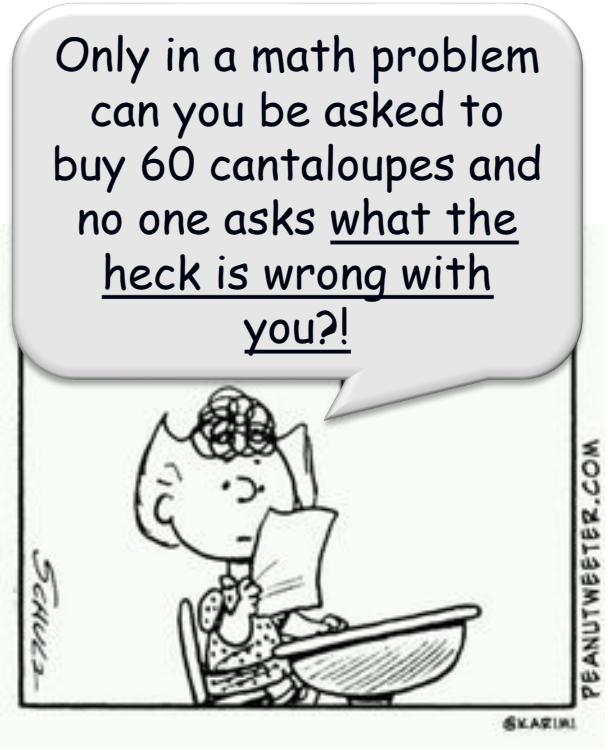


Any 3 or more component hazards confer a risk equal to:

1. Extant coronary disease – whether or not coronary disease is present, or
2. A frank diagnosis of Type2 Diabetes, whether or not diabetes is diagnosed.

Special Considerations for CMD Risk Determination
After SCI

- Obesity and insulin resistance are the greatest risks: generally co-morbid
  - Consider **postprandial hypertriglyceridemia secondary to sarcopenic obesity as serious**
- CMD-associated cardiocirculatory deficits and residual secondary impairments in persons with disability will render more challenging every aspect of daily activity, productivity, health, life quality, and independence.
- The CMD definitions are a **sterile, dichotomous calculus**, and omit population characteristics, needs, and considerations. **Risk assessment that doesn't consider the population-specific risk , isn't risk assessment….it's a math problem.**



Nash, MS, SL Groah, DR Gater, TA Dyson-Hudson, JA Lieberman, J Myers, S Sabharwal, AJ Taylor. Identification and Management of Cardiometabolic Risk after Spinal Cord Injury: Clinical Practice Guideline for Health Care Providers. *Top Spinal Cord Inj Rehabil* 24(4):379–423, 2018.

NIDILRR SCIMS Modular Grant:
Are we "Tooled" to Manage Cardiometabolic Health Disparities?

- n= 97 ♂and ♀ aged 18-63 years with all-cause SCI/D (C4-L1, AIS A-D) ≤ 2 months post-SCI
- 37% qualified for a diagnosis of CMD, although *no medications indicated ongoing treatment for obesity, dyslipidemia, or diabetes/insulin resistance.*
- 84% were overweight/obese by SCI population-specific criteria
- 44% were insulin resistant based upon AHA rules or HOMA v2.
- 55% were dyslipidemic
- Only 8/240 risk hazards we identified had been shared by health care professionals; obesity (1), Insulin resistance /diabetes (3), and hypertension (4).
- One subject asserted she was a diabetic and another hypertensive, but neither report was accurate.

- Spaulding Rehabilitation Hospital, Boston, MA;
- University of Miami Miller School of Medicine, Miami, FL;
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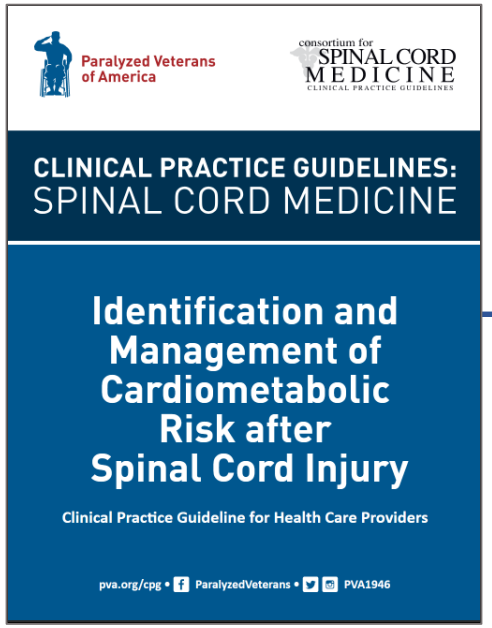
- Rancho Los Amigos National Rehabilitation Center, Downey, CA

NIDILRR SCIMS Grant #90SI5023; Nash, PI

Solinsky R, Betancourt L, Schmidt-Read M, Kupfer M, Owens M, Schwab JM, Dusseau II NB, Szlachcic Y, Sutherland L, Taylor JA, Nash MS. Acute Spinal Cord Injury is Associated with Prevalent Cardiometabolic Risk Factors. **Archives of Physical Medicine and Rehabilitation**. 2021 May 29.



Clinical Practice Guidelines: Identification and Management of Cardiometabolic Risk after SCI

An Evidence-Based Clinical Practice Guideline
Paralyzed Veterans of America
Consortium for Spinal Cord Medicine

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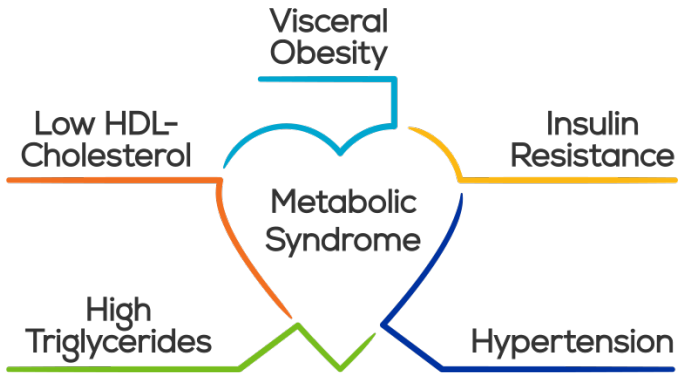
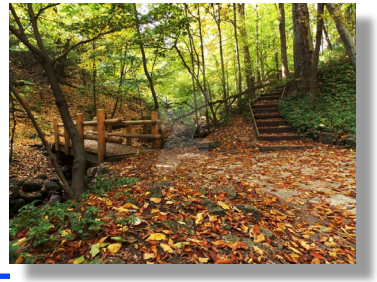
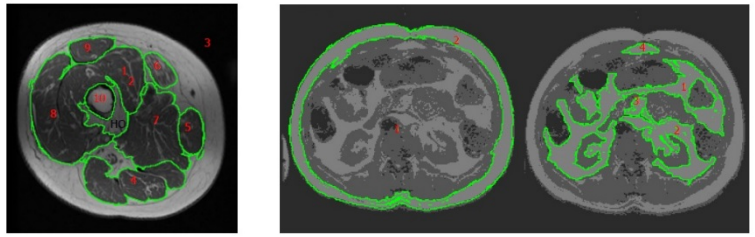


- Nash MS, Groah SL, Gater DR, Dyson-Hudson TA, Lieberman JA, Myers J, Sabharwal S, Taylor AJ. Identification and management of cardiometabolic risk after spinal cord injury. **The Journal of Spinal Cord Medicine**. 2019 Sep 3;42(5):643-77.
- https://www.pva.org/CMSPages/GetFile.aspx?guid=f3c29b7e-e201-4392-b241-9933dc620e40

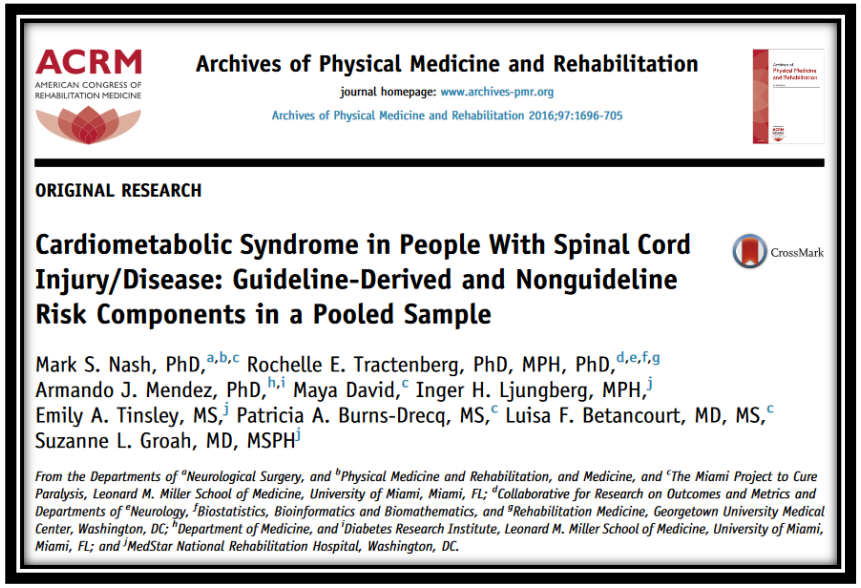
SCI Population Prevalence of Overweight/Obesity and Insulin Resistance: A Significant Guideline Concern



Gorgey AS, Wells KM, Austin TL. Adiposity and spinal cord injury. *World J Orthop* 2015; 6(8): 567-576 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i8/567.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i8.567



- Weaver et al., 2007
  - Using population-adjusted BMI's 68% of 7959 veterans with SCI/D were overweight/obese
- Nash et al., 2016
  - Using population-adjusted BMI's 83.1% of 379 non-veterans with SCI/D were overweight/obese.
  - 32% of subjects qualified for a guideline diagnosis of CMD



ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2016;97:1696-705

ORIGINAL RESEARCH

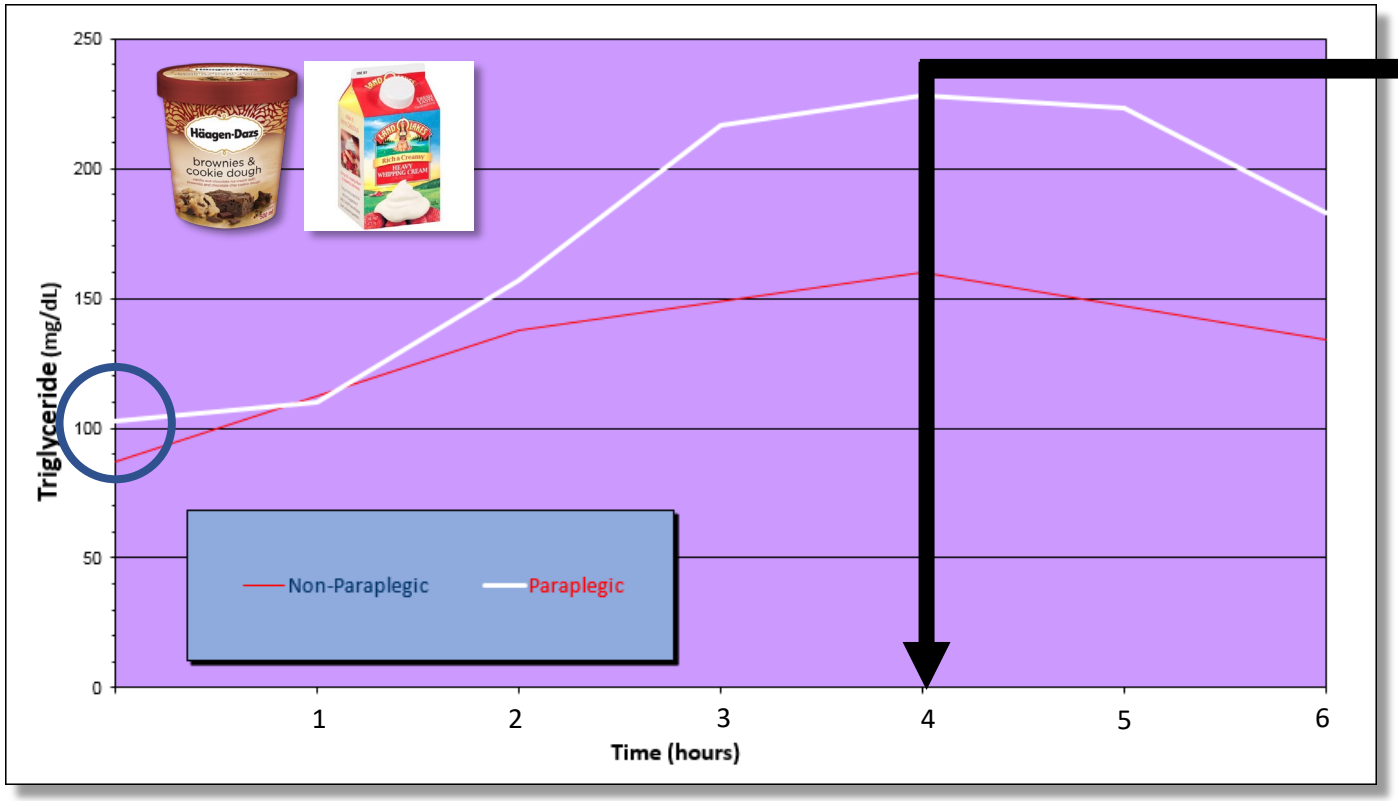
Cardiometabolic Syndrome in People With Spinal Cord Injury/Disease: Guideline-Derived and Nonguideline Risk Components in a Pooled Sample

CrossMark

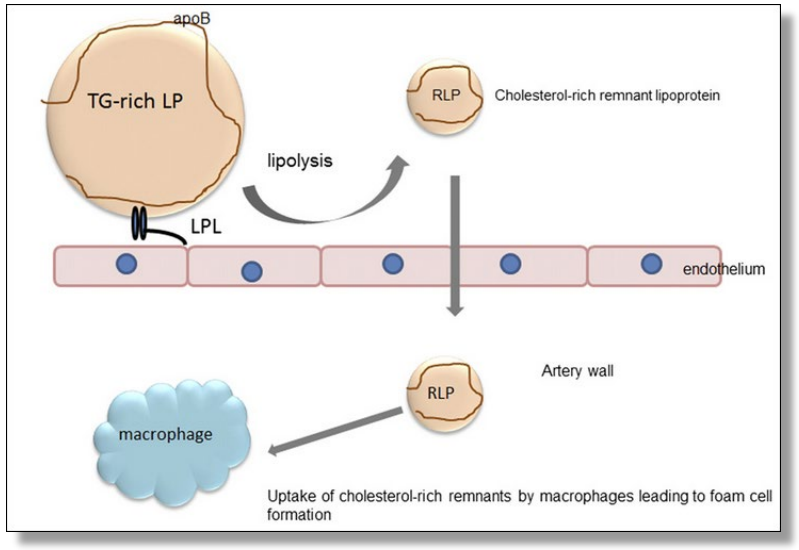
Mark S. Nash, PhD,[a,b,c] Rochelle E. Tractenberg, PhD, MPH, PhD,[d,e,f,g] Armando J. Mendez, PhD,[h,i] Maya David,[c] Inger H. Ljungberg, MPH,[j] Emily A. Tinsley, MS,[j] Patricia A. Burns-Drecq, MS,[c] Luisa F. Betancourt, MD, MS,[c] Suzanne L. Groah, MD, MSPH[j]

From the Departments of [a]Neurological Surgery, and [b]Physical Medicine and Rehabilitation, and Medicine, and [c]The Miami Project to Cure Paralysis, Leonard M. Miller School of Medicine, University of Miami, Miami, FL; [d]Collaborative for Research on Outcomes and Metrics and Departments of [e]Neurology, [f]Biostatistics, Bioinformatics and Biomathematics, and [g]Rehabilitation Medicine, Georgetown University Medical Center, Washington, DC; [h]Department of Medicine, and [i]Diabetes Research Institute, Leonard M. Miller School of Medicine, University of Miami, Miami, FL; and [j]MedStar National Rehabilitation Hospital, Washington, DC.

Evidence for an Exaggerated Post-Prandial Lipemia in Chronic Paraplegia: ***Muscle as a "Sink" for Blood-Borne Triglycerides***



Excessive blood-borne triglycerides oxidized to triglyceride-rich lipoproteins



Original Contributions

Evidence for an Exaggerated Postprandial Lipemia in Chronic Paraplegia

Mark Nash , PhD, Joris deGroot , MS, Alberto Martinez-Arizala , MD & Armando J. Mendez , PhD

Pages 320-325 | Received 11 Mar 2005, Accepted 15 Apr 2005, Published online: 02 Sep 2016

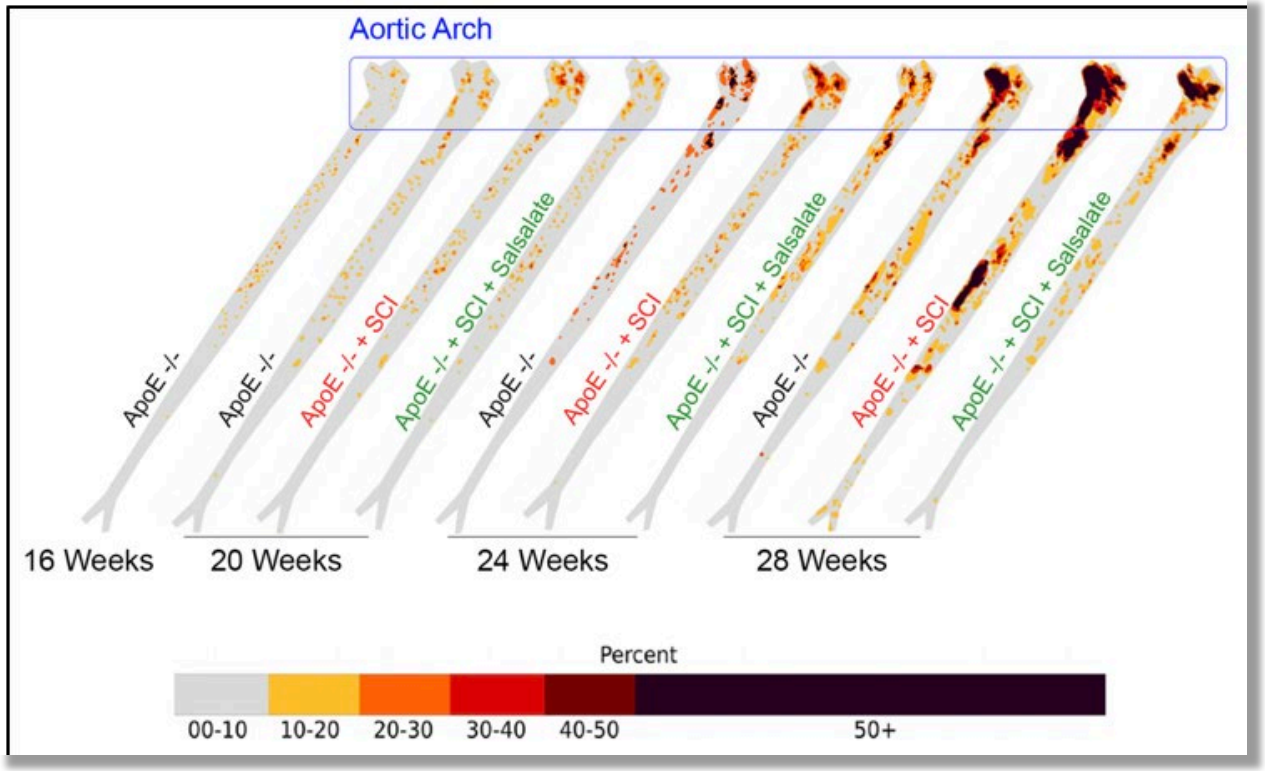
Download citation https://doi.org/10.1080/10790268.2005.11753827

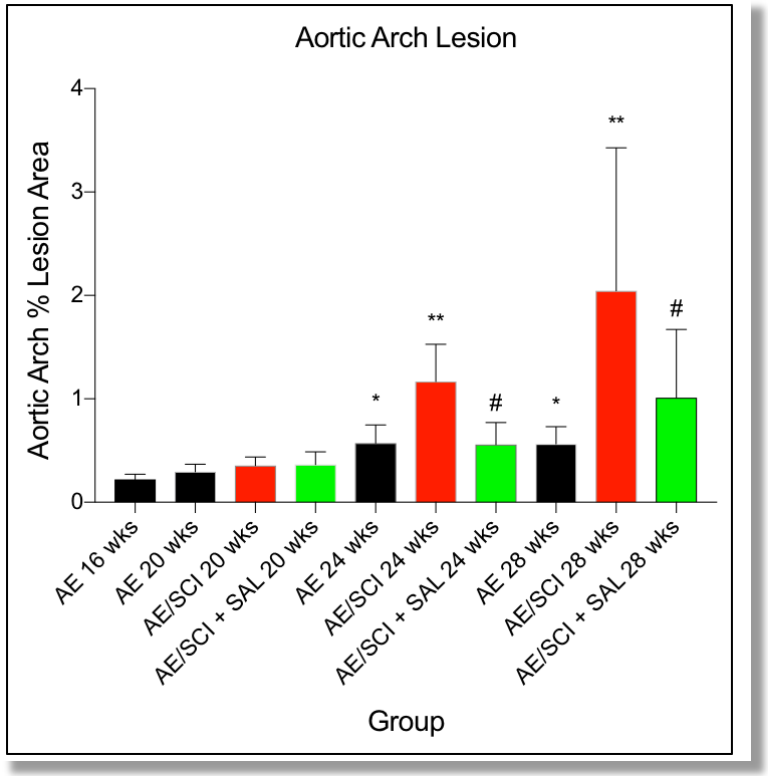
Nash M, DeGroot J, Martinez-Arizala A, Mendez, AJ. *J Spinal Cord Med*. 2005

Emmons, Garber, Cirnigliaro, et al. *J Am Coll Nutr*, 2010

Ellenbroek, Kressler, Cowan, Burns, Mendez, Palermo, Nash. *J Spinal Cord Med*, 2015

Accelerated Cardiometabolic Risks and Extant Atherosclerotic Disease in a Model of Spinal Cord Injury: Effects of an Anti-Inflammatory NF-kB inhibitor (Salsalate) in ApoE Knockout (C57BL/6 ApoE$^{-/-}$) Mice

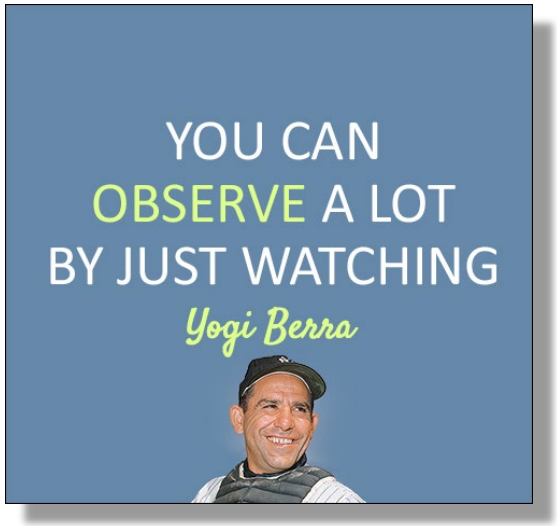




Bigford GE, Szeto A, Kimball J, Herderick EE, Mendez AJ, Nash MS. Cardiometabolic risks and atherosclerotic disease in ApoE knockout mice: Effect of spinal cord injury and Salsalate anti-inflammatory pharmacotherapy. ***Plos One***. 2021 Feb 24;16(2):e0246601.

Modifiable and *Non (or Quasi)-Modifiable* CMD Risk After SCI

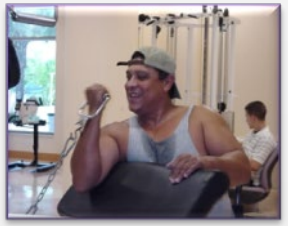
- Muscle atrophy
- Imprudent nutrition
  - Hypercaloric diet relative to daily need
  - Nutrition high in total fat (43% of kcal) and saturated fats
- Sedentary lifestyle either adopted, or imposed by SCI
- Pro-inflammatory atherogenic risk
- Functional sympathectomy accompanying injury above the levels of adrenal (at T6) or sympathetic (at T1) outflow.
- Age, gender, stress, genetics, susceptible endocannabinoid system, habit strength, loneliness, depression, environment, pre-morbid conditions, access to healthcare, caregivers and social relationships, and finances.



- Levine, Nash, Aronica. *Paraplegia*, 1992.
- Groah and Nash. *J Spinal Cord Med*, 2009.
- Kressler, Cowan, Bigford, and Nash. *Phys Med Rehabil Clin North Am*, 2014.
- Bigford and Nash. *Top Spinal Cord Inj Rehabil* 2017.

Modified National Cholesterol Education Project (NCEP) Adult Treatment Panel (ATP) III Guidelines: A Sequential Algorithm for Customized Management of Cardiometabolic Disease

1. Eliminate Drugs and Biologicals that worsen the CMD risk profile
2. Undertake Nutritional Modification
3. Incorporate Exercise
4. Consider Pharmacotherapy
5. **Consider Bariatric Surgery** ← **Last Resort**



RESEARCH ARTICLE | JANUARY 29 2009

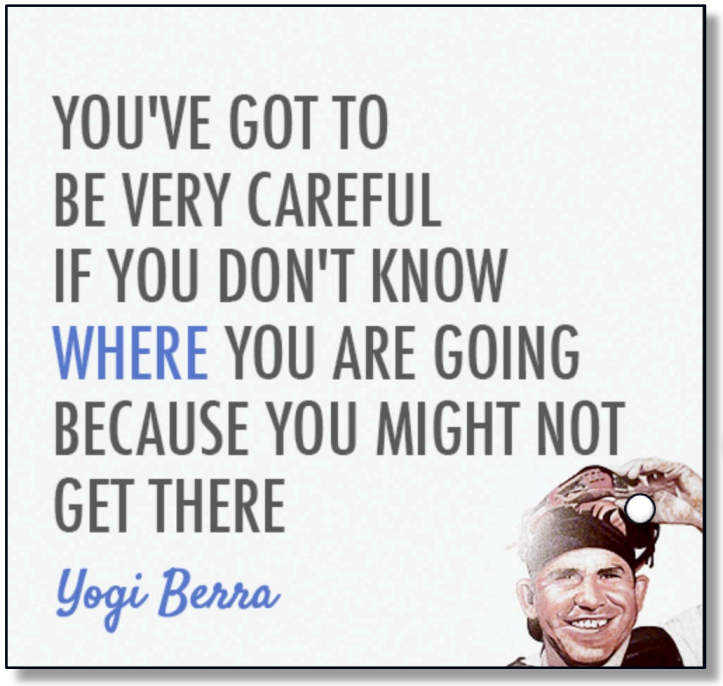
Guideline-Driven Assessment of Cardiovascular Disease and Related Risks After Spinal Cord Injury FREE

Trevor Dyson-Hudson; Mark Nash

Top Spinal Cord Inj Rehabil (2009) 14 (3): 32–45.

https://doi.org/10.1310/sci1403-32

Realistic Thinking for ‘Lifestyle Intervention’ – as Opposed to Either Nutrition or Exercise as Monotherapies



- Conventional wisdom says you can’t ‘out-run’ an imprudent diet to achieve CMD control. Conversely…
- Nutrition doesn’t provide all the benefits of exercise conditioning and attributes of fitness.

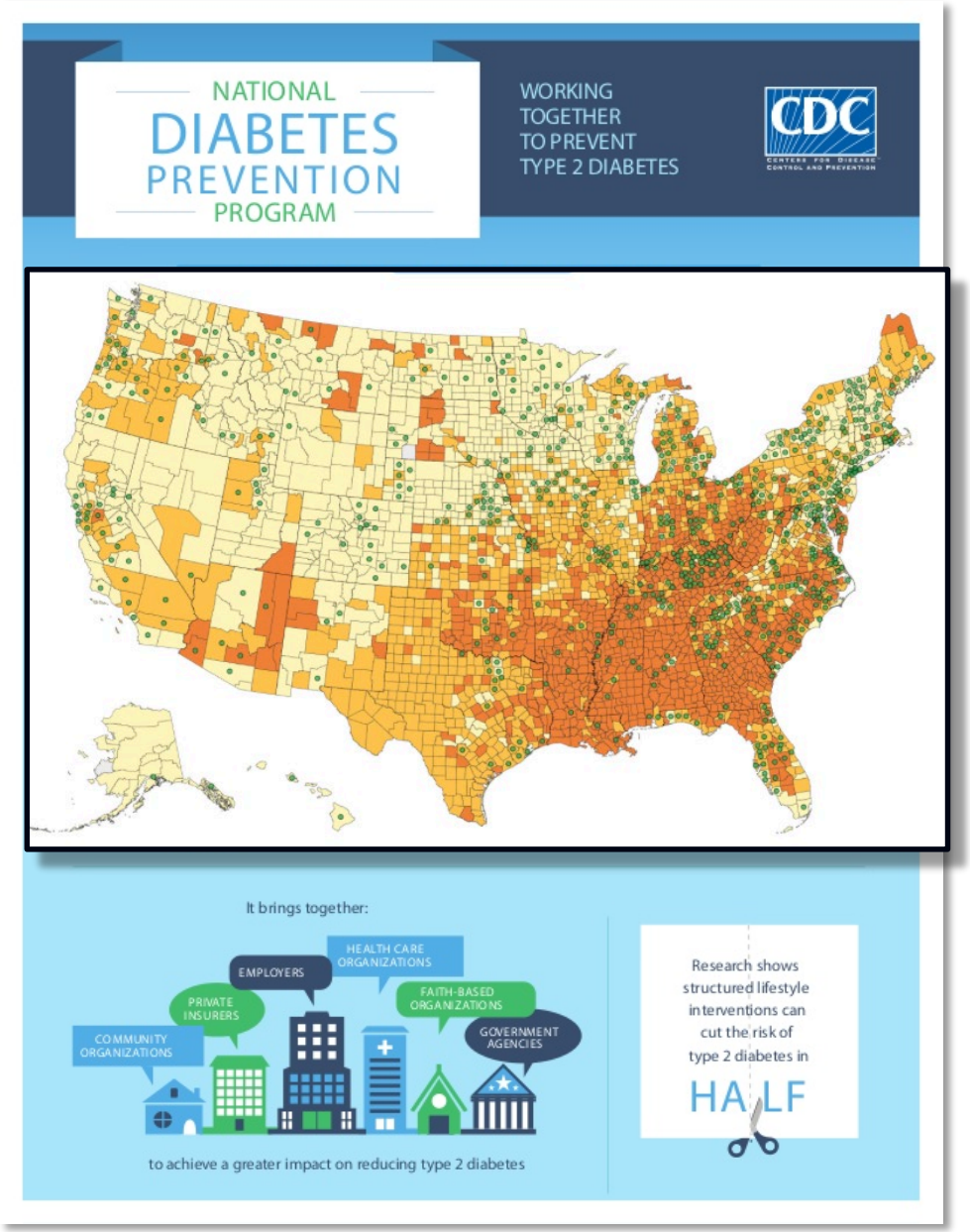
“ Lifestyle changes last about 2 weeks, and are soluble in alcohol…”

Mark Twain

Question: What's the Ten-year follow-up?

What are the options for Lifestyle Interventions in Individuals with ***Ambulatory Disabilities***?

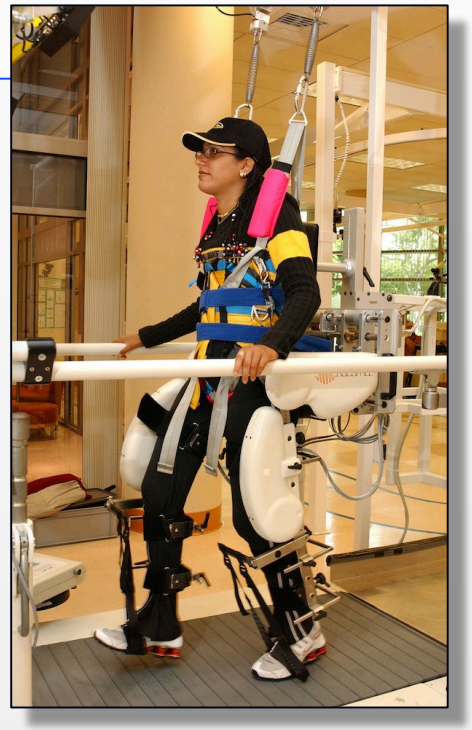
- 27 National Academic Medical Centers of the Diabetes Prevention Program used an LI of:
  - 10,000 steps/day
  - Mediterranean-style nutrition
  - Behavioral Integration
- The DSMB ended the study before reaching endpoints and fast-tracked publication of trial end-points.
- **Primary Finding**: A 7% reduction in body mass with LI reduced the risk for Type-2 diabetes by 58%, and was more effective than Metformin monotherapy. Ten year follow-up?
- The program benefits are durable and cost-effective, and amenable to modification for community-based, YMCA, race-specific, cross-cultural, socioeconomically challenged, and faith-based subpopulations.



What Do We Know About Effects of SCI on Nutritional Habits? Exercise Metabolism?

- Excessive in calories and saturated fat
- Worsened by lower metabolic rates associated with injures above T1 (i.e., functional sympathectomy)
- Overfeeding begins during rehabilitation and often becomes habit: Weight gain is greatest in months 2-7 post-SCI
- Combination strategies of exercise and nutrition are needed for weight and cardiometabolic disease management

Cowan and Nash. *Disability Rehabil,* 2010.



< 1000 kcal/day

Nash, Jacobs, Johnson, Field-Fote. *J Spinal Cord Med*, 2004

McMillan, Freeman, Bellman; Jacobs; Nash. Energetic and Hemodynamic Response to Electrical Stimulation Cycling in Persons with Paralysis. MSSE 49(5S):630, MAY 2017.

Fitness Deficits After SCI and TBI

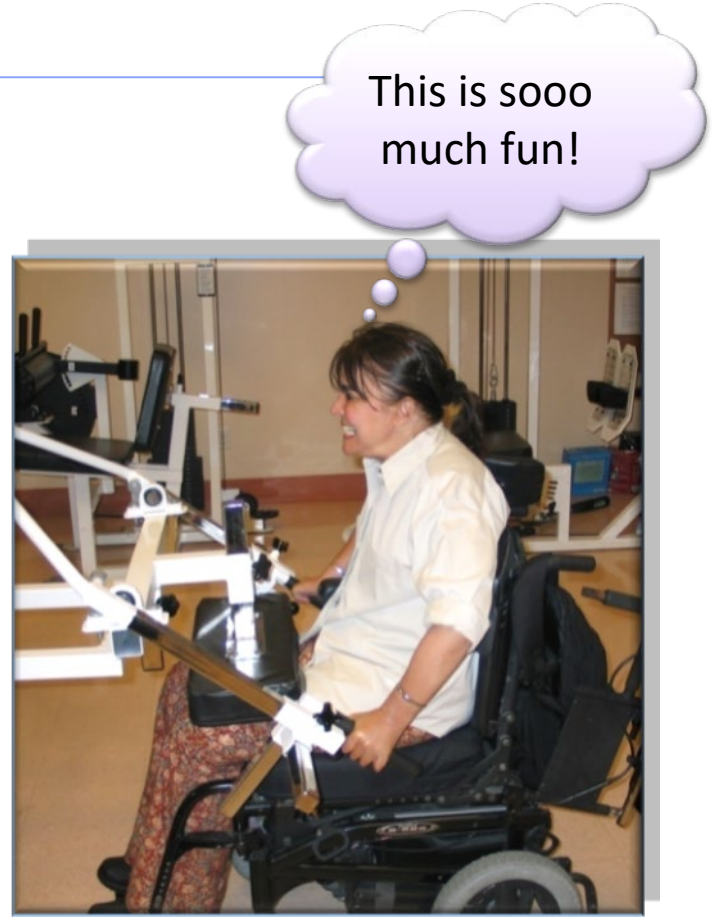
- Persons with SCI occupy the lowest segment of the human fitness continuum (Dearwater, 1986).
- Physical deconditioning commonly follows initial injury and often never recovers to pre-injury levels.
- The population is aging, which worsens the already poor fitness prognosis.
- Deconditioning poses medical, psychological, financial, **caregiver**, and societal challenges that can be reduced through positive health behaviors.

Nash M.S, DR Gater. Cardiometabolic Disease and Dysfunction Following Spinal Cord Injury: Origins and Guideline-Based Countermeasures. Phys Med Clin N Am 31(3):415-36, 2020.

Nash, M.S. and J.L. Bilzon. Guideline Approaches for Cardioendocrine Disease Surveillance and Treatment Following Spinal Cord Injury. In: Sadowsky C. (Ed.) Spinal Cord Injury Rehabilitation, Current Physical Medicine and Rehabilitation Reports (Springer Publishing), Current Physical Medicine and Rehabilitation Reports (2018) 6:264–276.

The ‘Best’ Exercise Prescription

- Safe
- Improves strength, anaerobic power, endurance, and flexibility
- Achieves musculoskeletal balance, while sparing shoulder pain and upper extremity decline
- Improves “function”
  - Enhance task performance and ease of ADLs
  - Improve homeostatic functions (i.e., orthostatic hypotension)
- Addresses CVD risk and cardiometabolic secondary complications
- Generates interest and compliance



Review article

Evidence-based and heuristic approaches for customization of care in cardiometabolic syndrome after spinal cord injury

Mark S. Nash, Rachel E. Cowan & Jochen Kressler

Pages 278-292 | Published online: 19 Jul 2013

Download citation https://doi.org/10.1179/2045772312Y.0000000034

Fitness Norms and Guidelines for Aerobic and Strength Conditioning after SCI

- SCI Action Canada
- World Health Organization
- U.S. DHHS (General Disabilities)
- APTA Physical Fitness for Special Populations Series
- NCHPAD
- American College of Sports Medicine
- PVA – Consortium for SCI Medicine

- Nash and Bilzon. *In* Spinal Cord Medicine (In Press) Kirshblum and Lin, [Eds], 2018.
- Simmons, Kressler, Nash. *Arch Phys Med Rehabil*, 2014.
- Martin Ginis, et al. *Spinal Cord,* 2018.
- Nash, Groah, Gater, et al. *Top SCI Rehabil*, 2018.

Rick Hansen Institute
Institut Rick Hansen

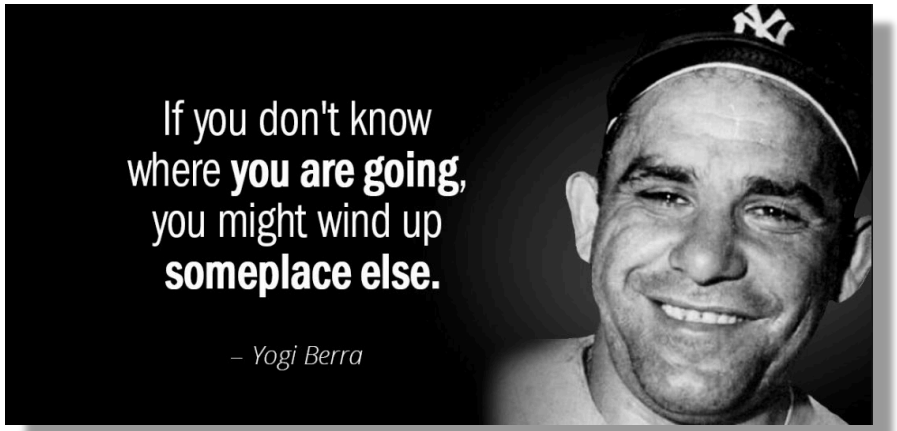
SCI ACTION CANADA

www.sciactioncanada.ca/guidelines

For important fitness benefits, adults with a spinal cord injury should engage in:
At least 20 minutes of moderate to vigorous intensity aerobic activity 2 times per week,
AND
Strength training exercises 2 times per week, consisting of 3 sets of 8-10 repetitions of each exercise for each major muscle group.

How…?	Aerobic Activity	Strength Training Activity
How often?	Two times per week	Two times per week
How much?	Gradually increase your activity so that you are doing at least 20 minutes of aerobic activity during each workout session.	Repetitions are the number of times you lift and lower a weight. Try to do 8-10 repetitions of each exercise. This counts as 1 set. Gradually work up to doing 3 sets of 8-10 repetitions of each exercise.
How hard?	These activities should be performed at a moderate to vigorous intensity. Moderate intensity: activities that feel somewhat hard, but you can keep doing them for a while without getting tired. Vigorous intensity: activities that make you feel like you are working really hard, almost at your maximum, and you cannot do these activities for very long without getting tired.	Pick a resistance (free weights, cable pulleys, bands, etc.) heavy enough that you can barely, but safely, finish 8-10 repetitions of the last set. Be sure to rest for 1-2 minutes between each set and exercise.
How to?	There are many ways to reach this goal, including: *Upper Body Exercises:* wheeling, arm cycling, sports *Lower Body Exercises:* Body weight supported treadmill walking, cycling *Whole Body Exercise:* recumbent stepper, water exercise	There are many ways to reach this goal, including: ■ Free weights ■ Elastic resistance bands ■ Cable pulleys ■ Weight machines ■ Functional electrical stimulation

Caveat: What Do The Guidelines 'Guide', and how "Guiding" are they?



- Fitness acquisition?
  - Yes
- Fitness acquisition for all attributes of fitness?
  - Probably not…what about anaerobic power?
- Dyslipidemia countermeasure?
  - Maybe, if sufficiently intense…
- All-cause CVD prevention, i.e., hard outcomes on MI, CVA, and sudden death?
  - Who knows? Never been tested…
- Dysglycemia and insulin resistance?
  - Likely…low hanging fruit.
- Functional (i.e., ADL) decline?
  - Not necessarily, because function isn't just a property of 'fitness', it's also skill.

Circuit Resistance Training Adapted for Persons with SCI

- 6 Resistance Maneuvers
- 10 repetitions; 6 Second lifts; 3 seconds concentric, 3 seconds eccentric
- Interposed periods of arm spinning after every 2 resistance maneuvers
- Maneuver changes within 10 seconds
- Repeat 3 times ≈ 43 minutes

Moser, Nash, Perry, LaPerriere, Goldberg. Effects of Aerobic Circuit Training on Adolescents with Well-Controlled Insulin-Dependent Diabetes Mellitus. *Arch Phys Med Rehabil*, 1998.

Circuit Resistance Training: Paraplegia

Effects of CRT on Peak Arm Endurance and Anaerobic Power of Subjects with Paraplegia (mean ± s.d.)

	Pre-Training	Post-Training	% Δ	p
VO_2 peak ($L \cdot min^{-1}$)	1.45 +/- 0.22	1.88 +/- 0.31	+ 29.7	<0.01
Time to Fatigue (sec)	624 +/- 195	816 +/- 223	+ 30.8	<0.01
Peak Power (Watts)	379 +/- 58	401 +/- 72	+ 5.8	<0.05
Mean Power (Watts)	254 +/- 43	276 +/- 50	+ 8.7	<0.05

Jacobs, Nash, Rusinowski. *Med Sci Sports Exerc,* 2001.

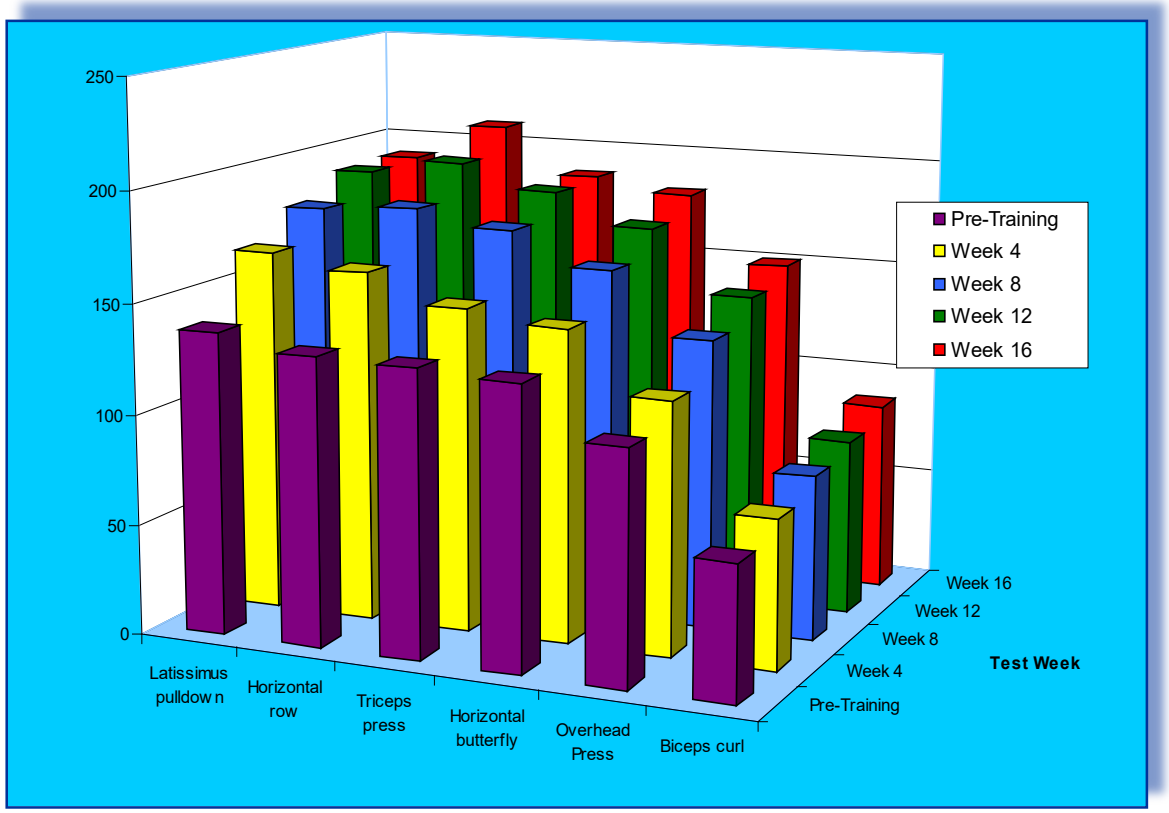
CRT Effects on Isoinertial One Repetition (1-RM) Maximal Strength in Subjects with Paraplegia (lb.)

Maneuver	Month 0	1	2	3	% Change
Shoulder Press	166.3	217.7	227.4	235	+ 41.3 **
Horizontal Row	190.5	206.1	233.0	238.3	+ 25.1 **
Horizontal Flexion	135.3	138.6	159.3	164.4	+ 25.5 **
Elbow Flexion	46.8	50.0	53.2	53.3	+ 13.8 *
Latissimus Pulldown	137.7	152.3	168.6	177.7	+ 29.0 **
Dips	142.3	152.3	161.7	167.9	+ 18.0 **

* $p < 0.05$
** $p < 0.01$

Jacobs, Nash, Rusinowski. *Med Sci Sports Exerc,* 2001.

The “Middle-Aged” Circuit: Effects Of CRT On Monthly Changes In One Repetition Maximal Strength

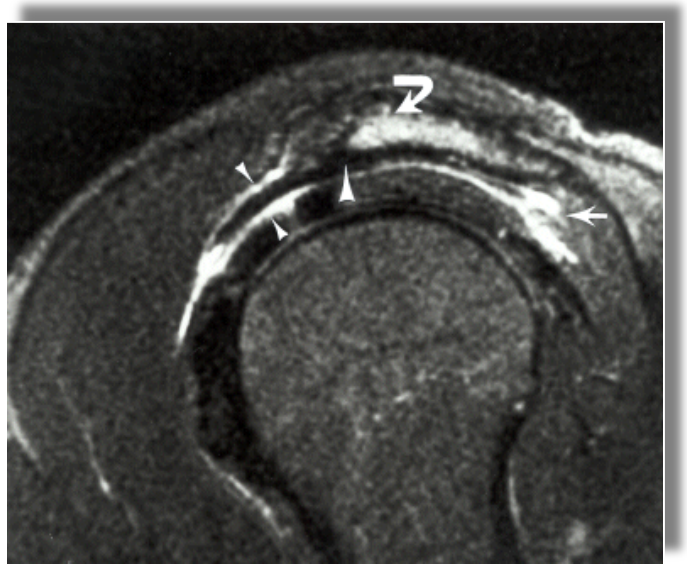


Maneuver	Change (%)
Overhead Press	38.6*
Horizontal Row	59.7*
Horizontal Butterfly	41.6*
Biceps Curl	41.4*
Latissimus Pulldown	38.6*
Triceps Press	44.0*

* $p < 0.01$

Nash, van de Ven, van Elk, Johnson. *Arch Phys Med Rehabil*, 2007.

Effects of CRT on Shoulder Pain in "Middle-Aged" Persons with Paraplegia: **An Inclusion Criterion**



	WUSPI Scores
Pre-Training	32.8 ± 23.5
Post-Training	5.0 ± 7.7 *

* p< 0.01

Nash, van de Ven, van Elk, Johnson. *Arch Phys Med Rehabil*, 2007.

Effects of CRT on Lipid Profiles of "Middle-aged" Persons with Paraplegia (mean ± s.d., n=9)

	Pre	Post	Change
TC (mg/dL)	183 ± 25.9	167 ± 32.7 *	- 16.4%
HDL-C (mg/dL)	40.5 ± 5.3	44.9 ± 5.6 *	+ 9.8%
LDL-C (mg/dL)	118 ± 22.2	88 ± 22.7 *	- 25.9%
TC:HDL Ratio	**4.5 ± 1.1**	**3.7 ± 0.7 ***	**- 0.8 Unit**
	50th %	**23rd %**	

* $p < 0.05$

Nash, et al. *J Spinal Cord Med* 2007.

Circuit Resistance Training Adapted for Persons with C5-C7 Tetraplegia

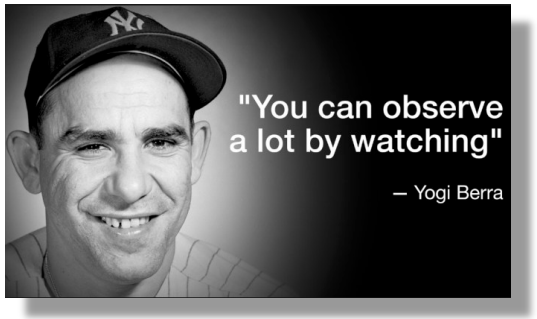
Resistance-Endurance Conditioning Exercise Improves Fasting and Postprandial Lipids, and Glycemic Regulation in 11 Men with Tetraplegia

Lowered the TC:HDL ratio by 7%.

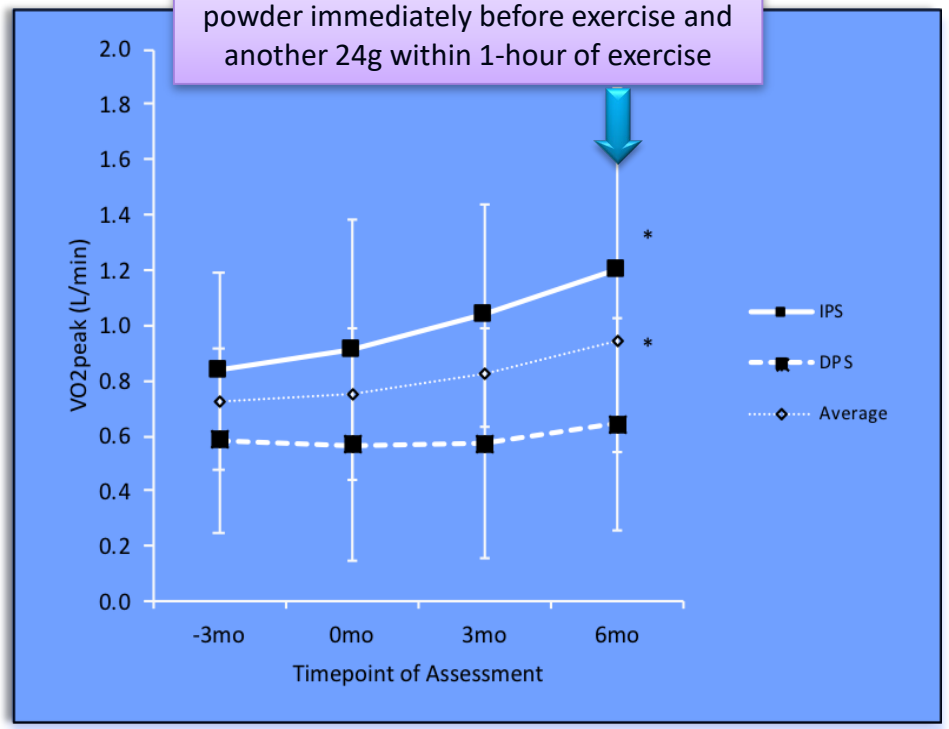
Improved insulin sensitivity (HOMA v2.) by 28%

Improved postprandial (AUC) triglycerides (52%), glucose (83%), and insulin (23%).

Lowered 2-hour post-load glucose by 27%.



With the addition of 24g of whey protein powder immediately before exercise and another 24g within 1-hour of exercise



Kressler, Jacobs, Burns, Betancourt, Nash. Effects of Circuit Resistance Training and Timely Protein Supplementation on Exercise-Induced Fat Oxidation in Tetraplegic Adults. *Top Spinal Cord Inj Rehabil*, 2014.

Exercise induced benefits may be augmented by appropriate dietary and feeding manipulations (From a few slides ago)

Citation: Spinal Cord Series and Cases (2017) 3, 17007; doi:10.1038/scsandc.2017.7

www.nature.com/scsandc

CASE SERIES

A lifestyle intervention program for successfully addressing major cardiometabolic risks in persons with SCI: a three-subject case series

Gregory E Bigford[1,2], Armando J Mendez[3,4], Luisa Betancourt[2], Patricia Burns-Drecq[2], Deborah Backus[5] and Mark S Nash[1,2,6]

Curriculum summary for behavioral intervention

	Session	*Topic*
Focus is on diet and exercise goals and education	1	Introduction to lifestyle intervention. Explain study goals.
	2	Introduce self-monitoring of weight at home.
	3	Teach 3 ways to eat less fat.
	4	Educate about healthy eating. Recommend alternate foods.
	5	Introduce physical activity modules.
	6	Tailor physical activity regimen to needs of the individual.
	7	Teach principles of energy balance between calories and exercise. Teach principles of health maintenance from exercise.
	8	Introduce principles of stimulus control as a method to prevent unhealthy eating. Introduce principles of stimulus control as a method to maintain exercise adherence.
Focus is on psychosocial and behavioral strategies	9	Present five-step model of problem solving.
	10	Introduce basic skills for eating and exercising away from home. Introduce basic skills for exercising away from home.
	11	Practice identifying negative thoughts and how to counter them.
	12	Introduce concept that slips are part of lifestyle change and provide tips for behavioral change maintenance.
	13	Introduce principles of aerobic fitness and coping with boredom.
	14	Provide strategies for managing social cues, both stressful and supportive.
	15	Summarize stress management principles presented over the course of the intervention.
	16	Focus on enhancing motivation and maintaining behavioral change post-lifestyle intervention.

Effects of an Exercise/Nutrition Behavioral Lifestyle Intervention on Cardiometabolic Component Risks in Persons with Chronic SCI(n=6)

	Study Timepoint			
Cardiometabolic Risk Factor	**Baseline**	**6 Month – Intense Supervision**	**12 Month – Minimal Supervision**	% Change
Body Mass (g)	108.9 (42.2)	98.7 (35.4)	97.6 (34.8)	- 10.4
Fasting Glucose (mg/dL)	117.0 (18.2)	101.0 (19.7)	105.7 (14.4)	- 9.7
HOMA-IR (v.2)	4.6 (1.3)	2.9 (0.6)	3.0 (1.4)	- 35.3
HDL (mg/dL)	33 (2.6)	37 (2.6)	38 (2.0)	+ 15.2
TG (mg/dL)	164.7 (37.4)	118.0 (69.9)	123.3 (64.5)	- 25.1

Citation: Spinal Cord Series and Cases (2017) **3**, 17007; doi:10.1038/scsandc.2017.7

www.nature.com/scsandc

CASE SERIES

A lifestyle intervention program for successfully addressing major cardiometabolic risks in persons with SCI: a three-subject case series

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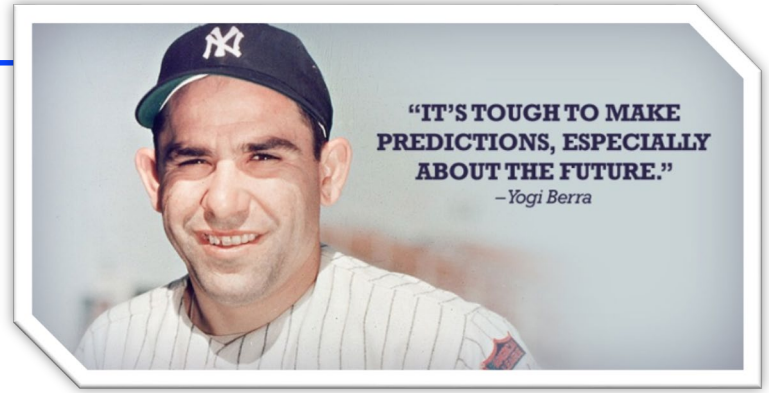
What can be done in cases where a disability precludes use of intensive Lifestyle Interventions?



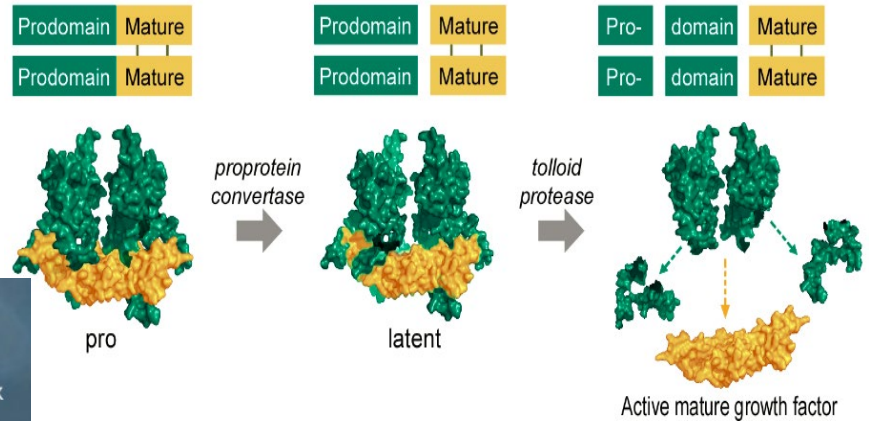
- Lower the intensity to a safe and tolerable level
  - Some physical activity may be better than none
  - The benefits of physical activity go beyond cardioendocrine disease…and consider the possibility for **different thresholds for benefit** on various outcomes.
  - Many benefits of physical activity inure to those who are in the low-moderate fitness range.

-or-

- **Don't undertake physical activity at all!**
  - ***Modify the molecular expression of muscle protein and muscle composition***

Myostatin Signaling: A Countermeasure to Sarcopenic Obesity

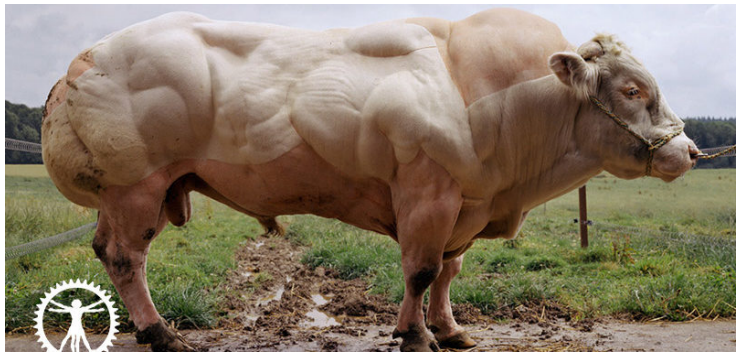
- **Myostatin** (growth differentiation factor 8, GDF-8 Gene Superfamily) is a **myokine**, a protein produced and released by myocytes that acts on muscle cells' autocrine function to **inhibit myogenesis**: muscle cell growth and differentiation.

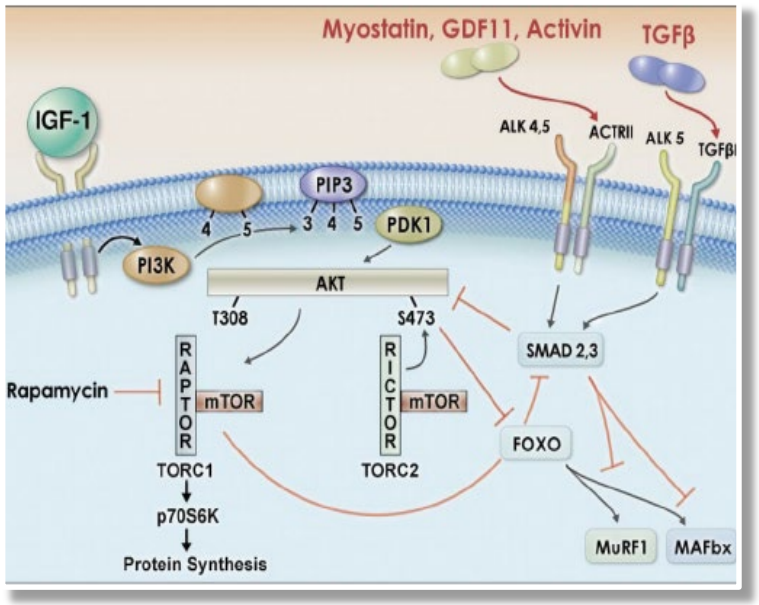


SCHOLAR ROCK

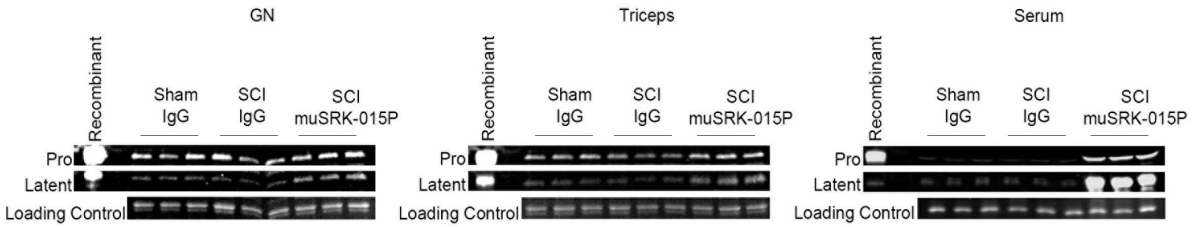
McPherron, et al, Nature 1997

Belgian Blue; Mstn^{-}/Mstn^{-}



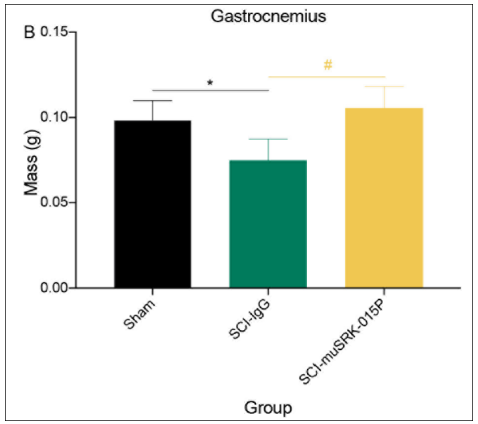


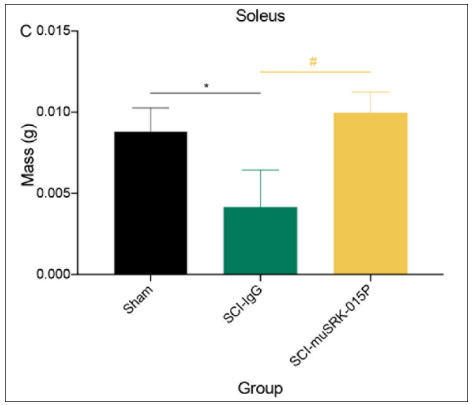
Pharmacological Inhibition of Myostatin with SRK-015 Improves Key Characteristics of Muscle Pathology in a Severe Contusion Model of SCI



Target engagement of SR-015 in Gastrocnemius, Soleus, and Serum.

Representative Soleus muscle masses from sham, control (2 types), and SRK-015-treated mice (C57BL/6). n=8/group)

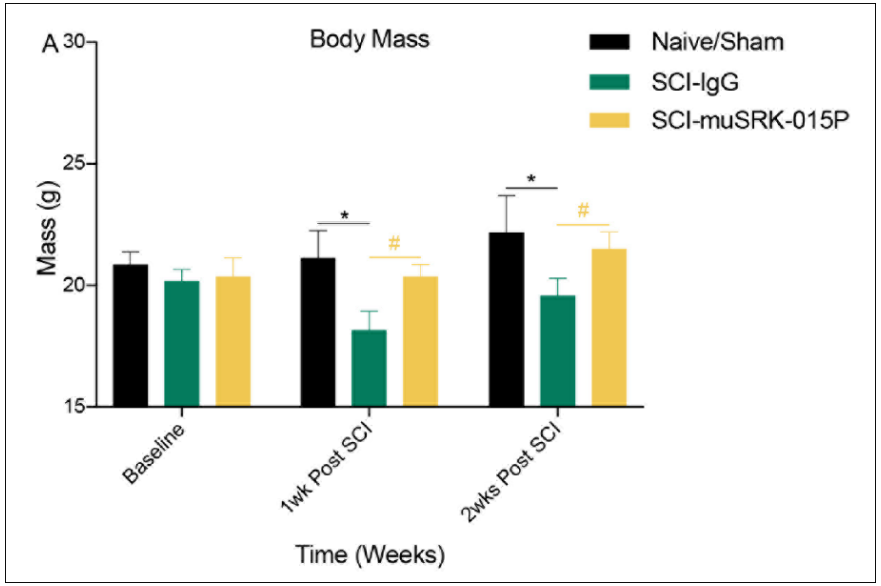


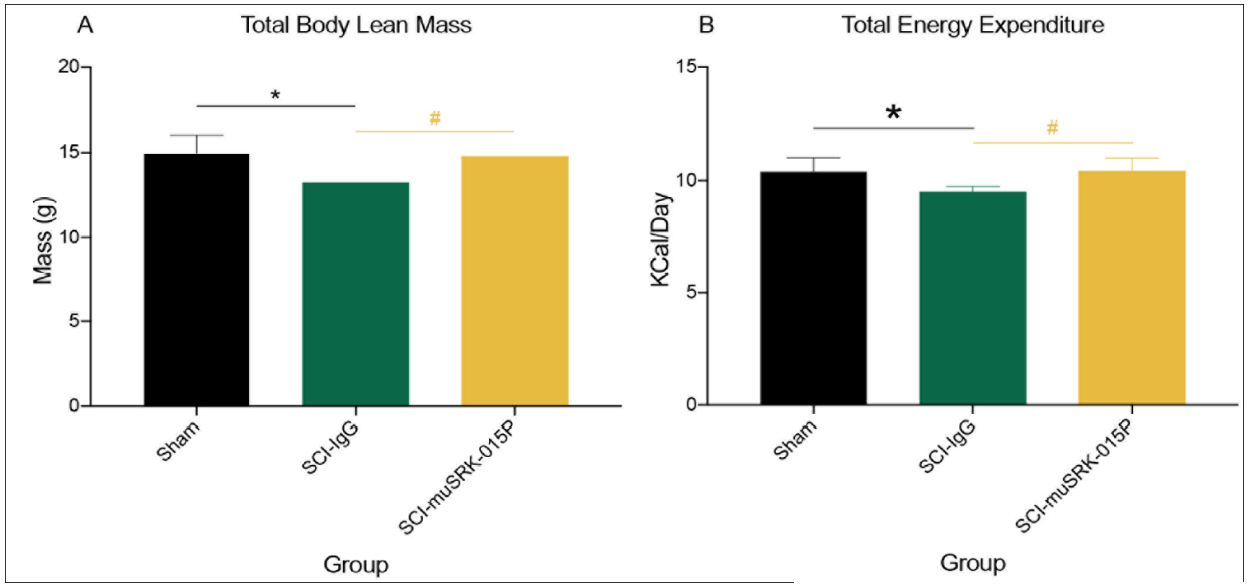


Bigford GE, Dietrich WD, Webster M, Donovan A, and MS Nash. Pharmacological Inhibition of Myostatin in a Contusion Model of Spinal Cord Injury. ***J Neurotrauma*** 34 (13): A75, 2017. DOI: 10.1089/neu.2017.29011.abstracts

Bigford GE, A Donovan, M Webster, WD Dietrich, and MS Nash. Selective myostatin inhibition spares sublesional muscle mass and myopenia-related dysfunction following severe spinal cord contusion in mice. **J Neurotrauma** (*In Press, September 2021*).

Effects of SRK-015 on C57 Blk/6 Mice with Severe Contusion SCI

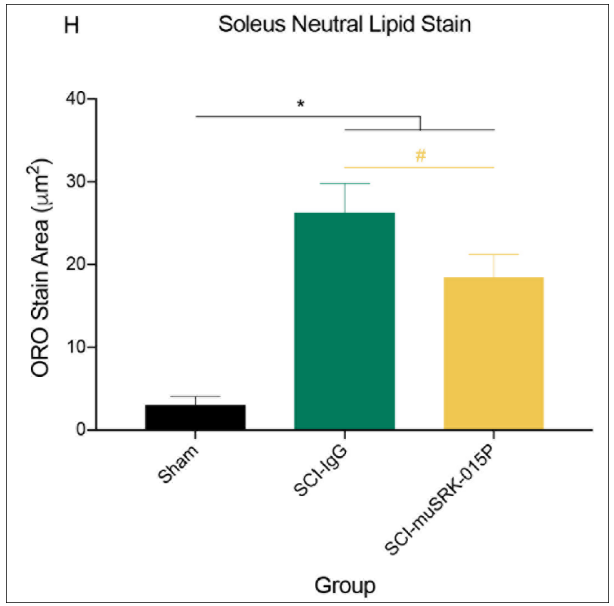


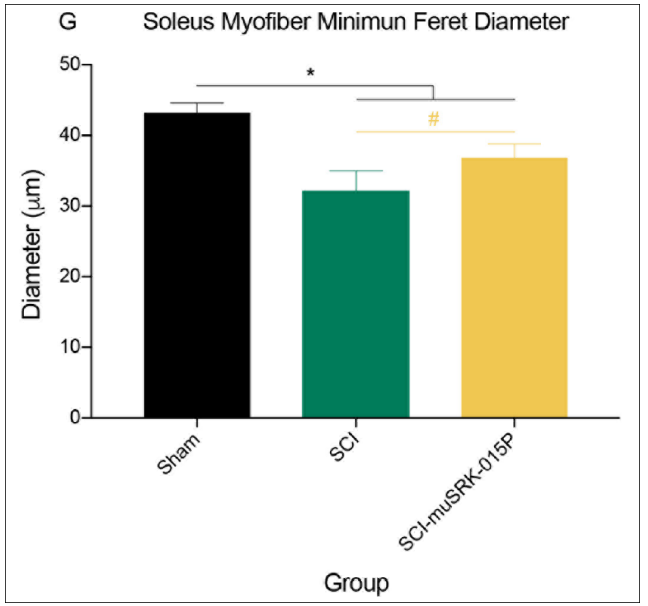


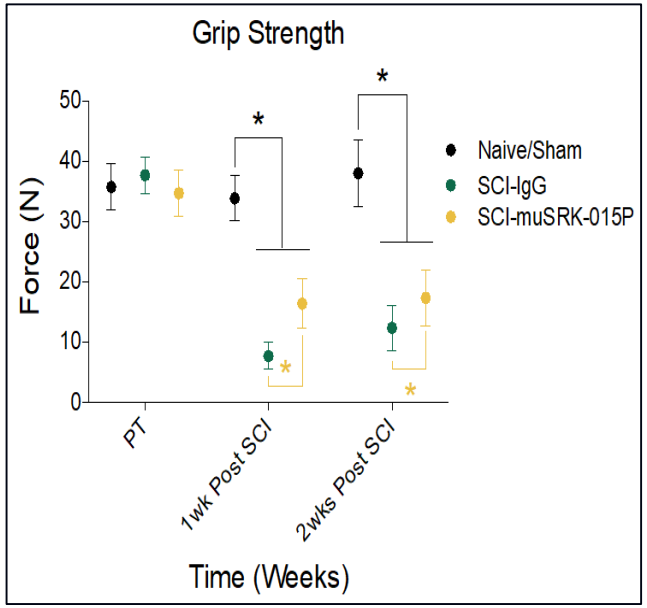
Effects of Myostatin inhibition by SR-015 on total body mass and lean body mass with experimental SCI and Controls. (n=8/group)

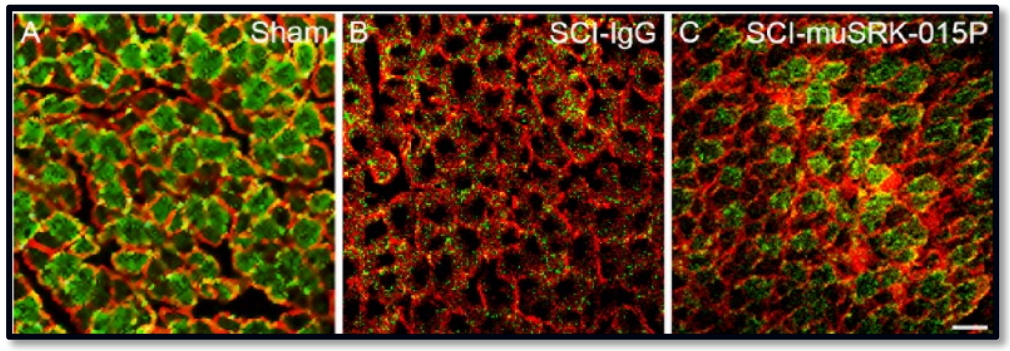
Effects of SR-015 on caloric expenditure derived from testing in metabolic chambers. (n=8/group)

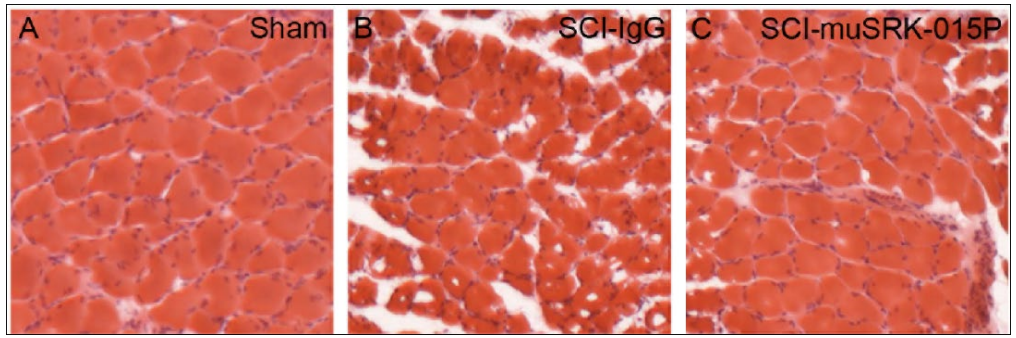
Effects of Myostatin Inhibition (SRK-015) on Skeletal Muscle following Severe Spinal Cord Contusion











Phase 3 Human Testing of SRK-015 Targeted for Children with SMA

SRK-015 FOR SPINAL MUSCULAR ATROPHY (SMA)

SRK-015 FOR SMA | UNMET NEEDS FOR SMA

SRK-015, our most advanced drug candidate, is a selective and local inhibitor of latent myostatin. Scholar Rock is developing and investigating SRK-015 as a treatment to improve muscle strength and motor function in patients with Spinal Muscular Atrophy (SMA).

Myostatin is a member of the TGFβ superfamily of growth factors and is expressed primarily in skeletal muscle cells to inhibit muscle growth. In the body, it works in concert with other growth factors and hormones to maintain appropriate muscle mass. There has been an emerging interest in therapeutically targeting myostatin following the discovery of myostatin-deficient animals that have increased muscle mass and strength.

SRK-015 uniquely targets the latent form of myostatin, specifically blocking its activation in muscle. Inhibiting the supracellular activation of myostatin, rather than the traditional approach of blocking already activated, mature myostatin or the myostatin receptor, avoids blocking the activity of other closely-related members of the TGFβ superfamily that may lead to undesirable side effects.

Development Plans

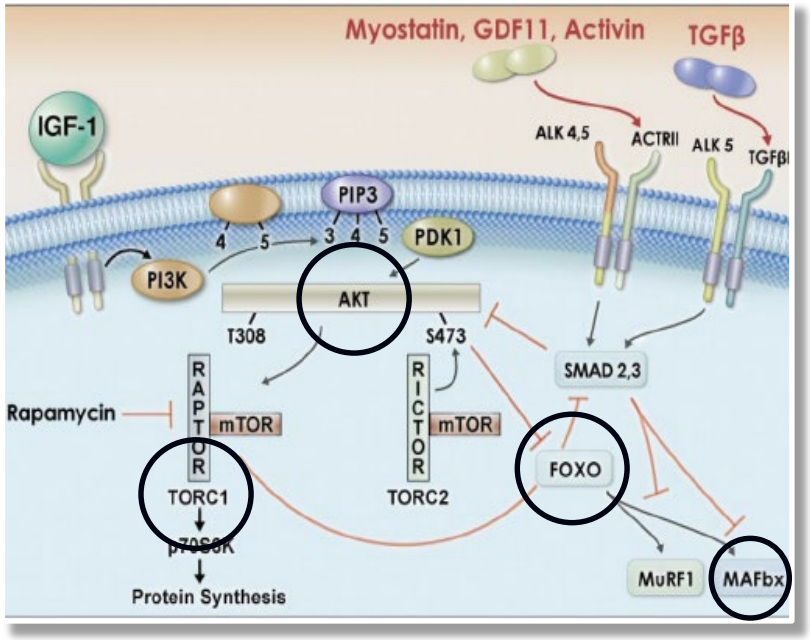
Scholar Rock is advancing SRK-015, a first-in-class selective inhibitor of the activation of myostatin, into clinical development for the treatment of SMA. We have initiated a Phase 1 clinical trial and intend to commence a Phase 2 trial in patients with later-onset SMA in the first quarter of 2019. We believe that SRK-015 has the potential to be the first muscle-directed therapy to reverse or prevent muscle atrophy in SMA patients and could be used both as a monotherapy or together with the current standard of care.

W81XWH1810775
Award Mechanism: Department of Defense Health Program, Congressionally Directed Medical Research Programs, Spinal Cord Injury

Selective Pharmacological Inhibition of Myostatin with SRK-015P in a Contusion Model of SCI: Effects on Obesity, Muscle, and Cardioendocrine Pathology

Naturally Occurring Lipophilic Pentacyclic Triterpenoid - Ursolic Acid (UA)

- Low toxicity herb found in apples, rosemary, and thyme.
- UA enhances insulin- and IGF-mediated phosphorylation of AKT, S6K1 and FOXO1 in skeletal muscle.
- UA inhibits skeletal muscle atrophy associated with denervation and induces skeletal muscle hypertrophy in the absence of an atrophy stimulus.
- UA augments muscle strength and stimulates mTOR-C1 signaling in skeletal muscle.



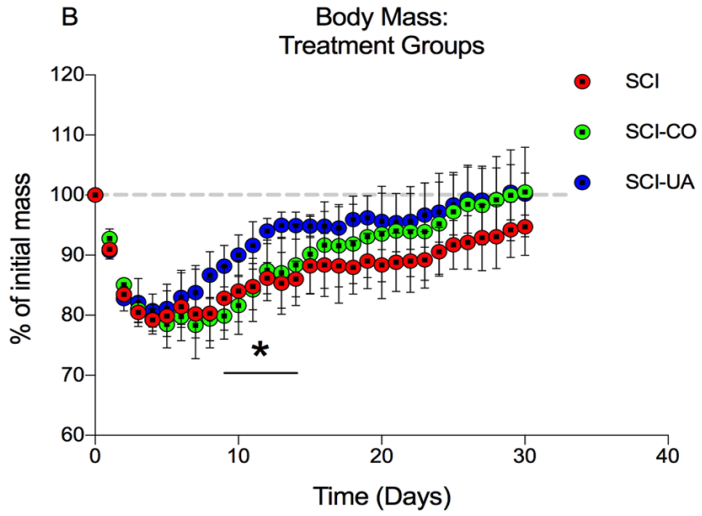
RESEARCH ARTICLE

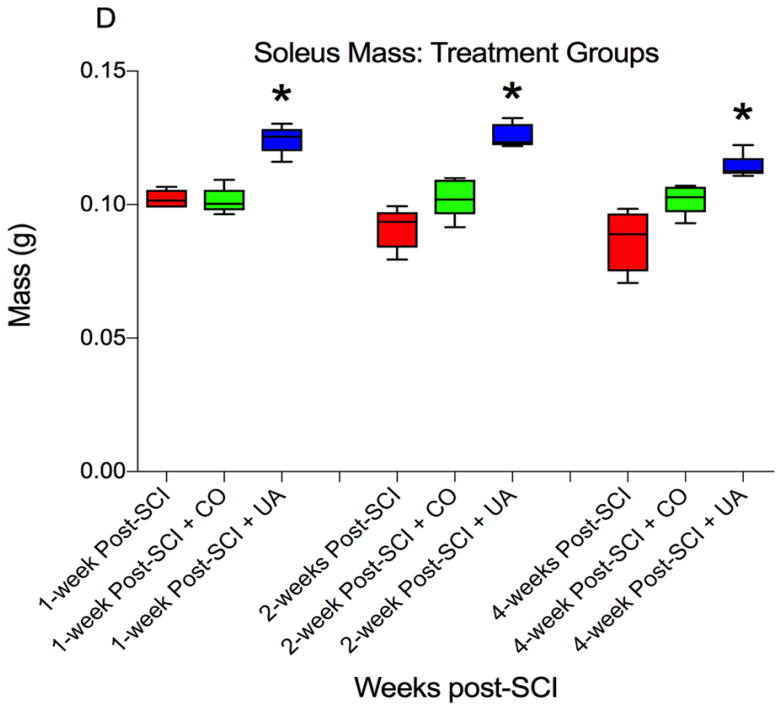
PLOS ONE

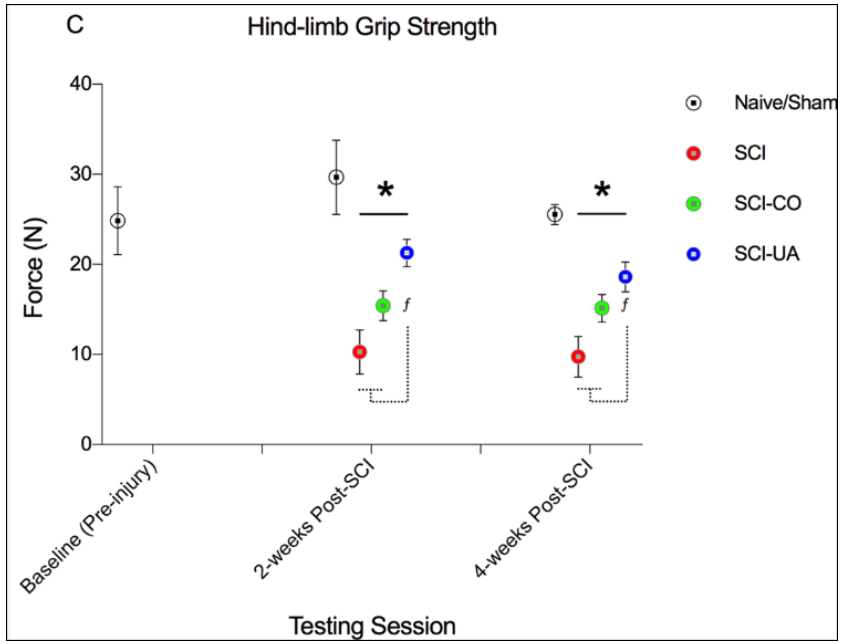
Effects of ursolic acid on sub-lesional muscle pathology in a contusion model of spinal cord injury

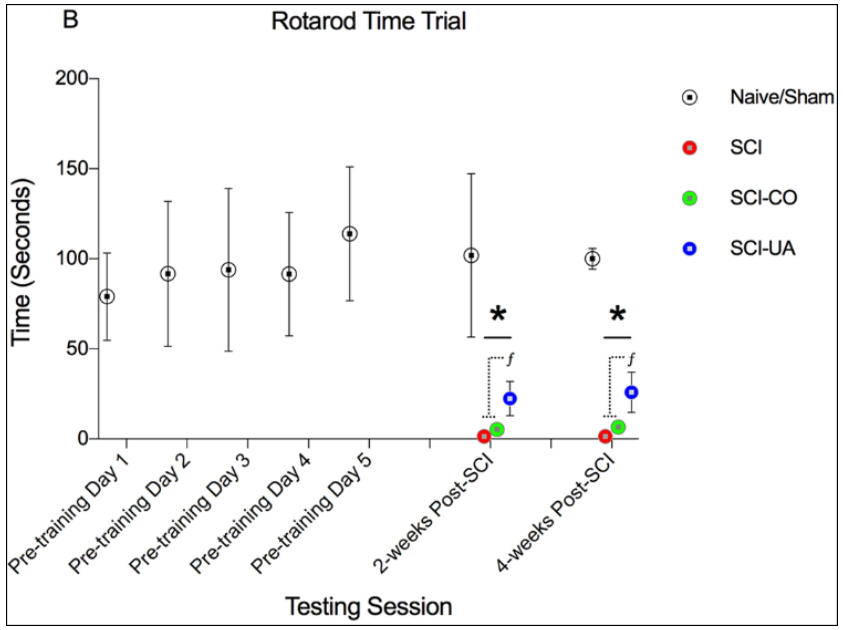
Gregory E. Bigford, Andrew J. Darr, Valerie C. Bracchi-Ricard, Han Gao, Mark S. Nash, John R. Bethea

Published: August 29, 2018 • https://doi.org/10.1371/journal.pone.0203042





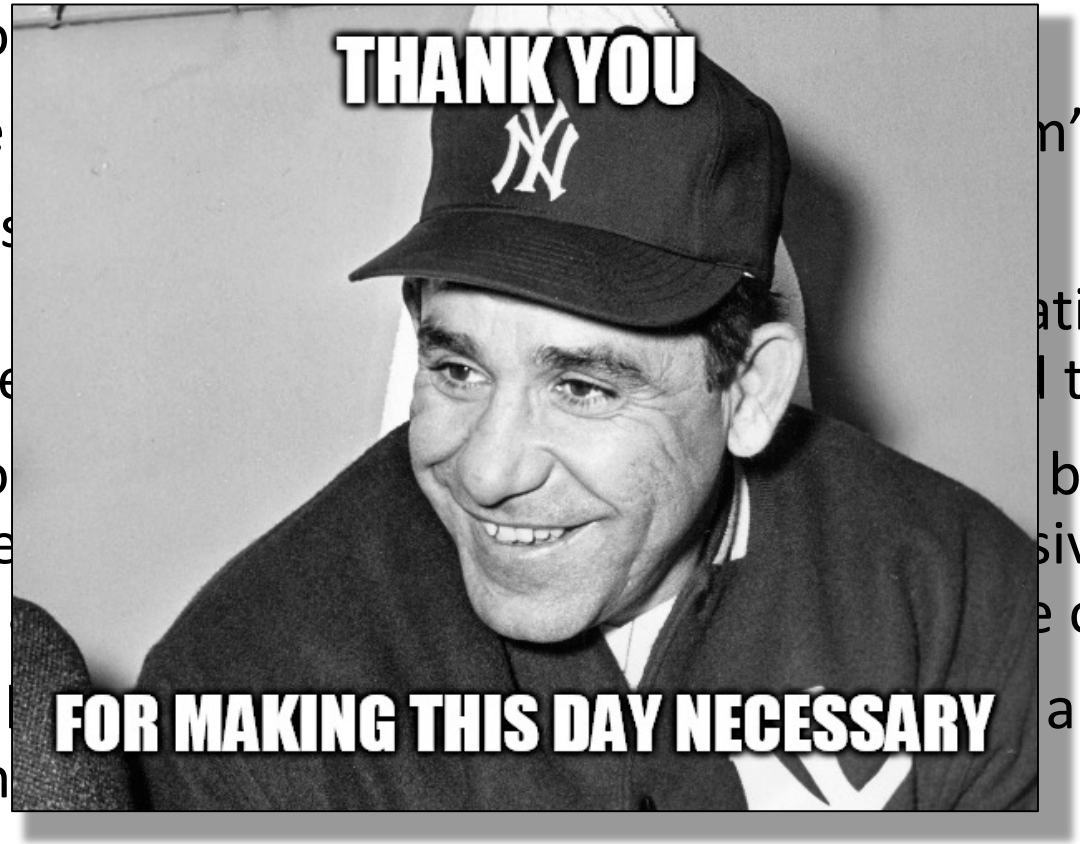




motor coordination, balance and motor learning

Conclusions and a Goal Verification Check!

- ✓ The Cardiometabo
- ✓ We've defined the m' after SCI.
- ✓ Data has been pres
  - ✓ Consequences atisfaction, productivity, he l their caregivers.
- ✓ We know what wo but maybe not yet for all. Exercise like sive role in this process. Nutrition e overlooked!
- ✓ New methods are and better serve all with disabilities an



- ✓ End with a Berra-ism