What Nutritional and Metabolic Strategies Actually Improve Surgical Outcome in Orthopedic Surgery Patients?

Oregon Association Orthopaedic Surgeons
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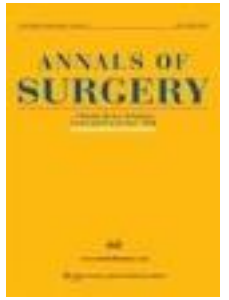
Disclosures:

- **I have no relevant financial relationships with ineligible companies to disclose.**

Recent Surgical Nutrition Literature is Very Confusing ?

- Early vs Late PN / Nutrition -Van den Berghe G (NEJM 2011)
  - EPNic Trial: Nutritional intervention shuts off "autophagy" ?
- Trophic vs full feeds - Rice T (JAMA 2012)
  - How much is enough
- Redox trial - Heyland DK (NEJM 2013)
  - Intervention with high dose GLN is harmful in "real sick" people ?
- Supplemental PN- Heidigger (Lancet 2013)
  - Supplemental PN "may" benefit , but now it appears probably not
- PN = EN ? Harvey S (NEJM 2014)
  - No benefit of EN over PN
- PN better than EN ?- Reignier (Lancet 2018)
  - Nutrirea 2 : Less bowel ischemia, vomiting. But started EN in 3 days with crossover
- Resolving inflammation is active process- Serhan (Nature 2014, JCI 2018)
  - Resolvins, Protectins, Maresins (SPMs)
- The science behind the "microbiome" Alverdy (JACS 2018)
  - Microbiome converts to pathobiome
- Full vs reduced calories in the ICU (ANZICs NEJM 2018)
  - Hypocaloric feeding
- Autophagy – influence on nutrition delivery (Ann NY Acad Sci 2020)
  - Timing of starting nutrition may be key
- Newer studies (presented at ASPEN, ESPEN, and PENSA 2022, 2023)
  - Effort Trial, Sustain trial , RE-Energize trial, etc ?
    - NO benefit of higher protein, additional Se in cardiac surgery, glutamine in burns etc



Surgeon Modifiable Factors for Preventing Complications and Optimizing Outcomes

AMERICAN COLLEGE OF SURGEONS
Inspiring Quality: Highest Standards, Better Outcomes
100+years

STRONG for SURGERY

Nutrition | Glycemic Control | Smoking Cessation | Medicines

ERAS® Society
www.erassociety.org

Goals:
- Reduce stress
- Reduce complications
- Reduce length of stay

Pre-op

- Glycemic control
- Smoking cessation
- Nutrition
  - Metabolic prep (Arg/FO)
  - Pre and probiotics
  - CHO loading
  - protein/AA supplements
  - Resistance exercise + protein
    - "prehabilitation"
- Clearing MRSA
- N/V Prophylaxis
- Weight loss
- Cardiac clearance
- Pulmonary
- Geriatric consult if > 70yo

Immediate Peri-op

- Skin prep selection
- Antibiotics
- Glycemic control
- Placement of feeding tubes
- Intra-op warming ?
- Normothermia
- Suture choice
- Closure methods
- Minimize tubes/drains
- MIS surgery
- DVT prophylaxis
- Techniques
  - Halsted principles

Post-op

- DVT prevention protocol
- NPWT
- minimize narcotics
- Early PO intake
- Early enteral feeding
  - start slow and advance
  - gradual increase in protein
- Resistance exercise
- Fish Oils (EPA and DHA)
  - SPMs
- Probiotics
  - Results in lower systemic inflammation
  - Helps maintain epithelial integrity
  - Prevention C.diff, AAD
  - preventing conversion of microbiome to pathobiome

Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Total Hip and Knee Arthroplasty in the Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol in Elective Total Hip and Knee Arthroplasty Study (POWER2)

JAMA Surgery 2020

Javier Ripollés-Melchor, MD[1,2,3,4]; Ane Abad-Motos, MD[1,2,3,4]; Yolanda Díez-Remesal, MD, PhD[5] ; et al

What components of the Orthopedics ERAS protocol (16 items) improved outcome in THA and TKA?

Regional or local analgesia
Anemia and bleeding management
Early mobilization

	ERAS included individual items	Definitions of ERAS Compliance for Included individual items
1	Presurgical education	Received verbal and written ERAS education at a dedicated preadmission visit
2	Presurgical optimization	Patients stopped smoking 4 weeks before surgery and alcoholics ceased all alcohol consumption 4 weeks before surgery.
3	Preoperative fasting	Pre-operative fasting limited to 2 hours for clear liquids (water, coffee, juice without pulp); and at 6 hours for solids.
4	Patient Blood Management	Set of measures applied to optimize preoperative hemoglobin, avoid bleeding and avoid transfusion
5	Preoperative carbohydrate drinks preload	Given preoperative carbohydrate drink. Defined as at least 50 g carbohydrate in at least 400 mL fluid in the form of a dedicated preoperative beverage with a proven safety profile. Given up until 2 hours before anesthesia.
6	Avoidance of long-acting sedative premedication	No long acting sedative premedication given (eg, opioids, sedative antihistamines, and neuroleptics)
7	Thromboprophylaxis	Given thromboprophylaxis. Low-molecular-weight heparin and compression stockings
8	Antibiotic prophylaxis	Given antibiotic prophylaxis before skin incision
9	Regional anesthesia	Anesthetic procedure that allows rapid awakening, adequate analgesia and patient recovery. The item is considered positive provided that any major anesthetic technique (spinal anesthesia or general anesthesia) is accompanied by local or locoregional anesthesia techniques; or continuous epidural anesthesia
10	PONV prophylaxis	Given PONV prophylaxis
11	Active prevention of unintentional hypothermia	Use of fluid heaters and / or thermal blanket for all patients during the surgical procedure
12	Goal Directed Fluid Therapy	Intravenous fluid administration guided by hemodynamic goals. Based on cardiac output or derived monitoring by any validated cardiac output monitoring.
13	Postoperative analgesia	A multimodal analgesic management that includes at least 2 drugs in order to avoid or reduce the administration of morphics.
14	Postoperative glycemic control	Patients receive glycemic control in the first 24 hours. For target glycemia <180g / dl
15	Early mobilization	Defined as the patient move at least to armchair in the first 12 postoperative hours.
16	Early feeding	Defined as the patient tolerates oral feeding in the first 6 postoperative hours.

What can you do today ?

- Nutrition consult
- Prehabilitation Program
  - Focus to specific populations
- Anti-inflammatory diet
- Specifics
  - Protein
    - Benefit significantly improved when combined with resistance exercise
  - Fish oils
  - Pre and Probiotics
  - Nutritional supplements

Objectively Defining Risk

- **NSQIP surgical risk calculator** (Cohen ME JACS 2017)

- **Orthopedic frailty risk stratification (OFRS)**
  Gupta NK et al J Orthopaedic Surgery and Research 2025

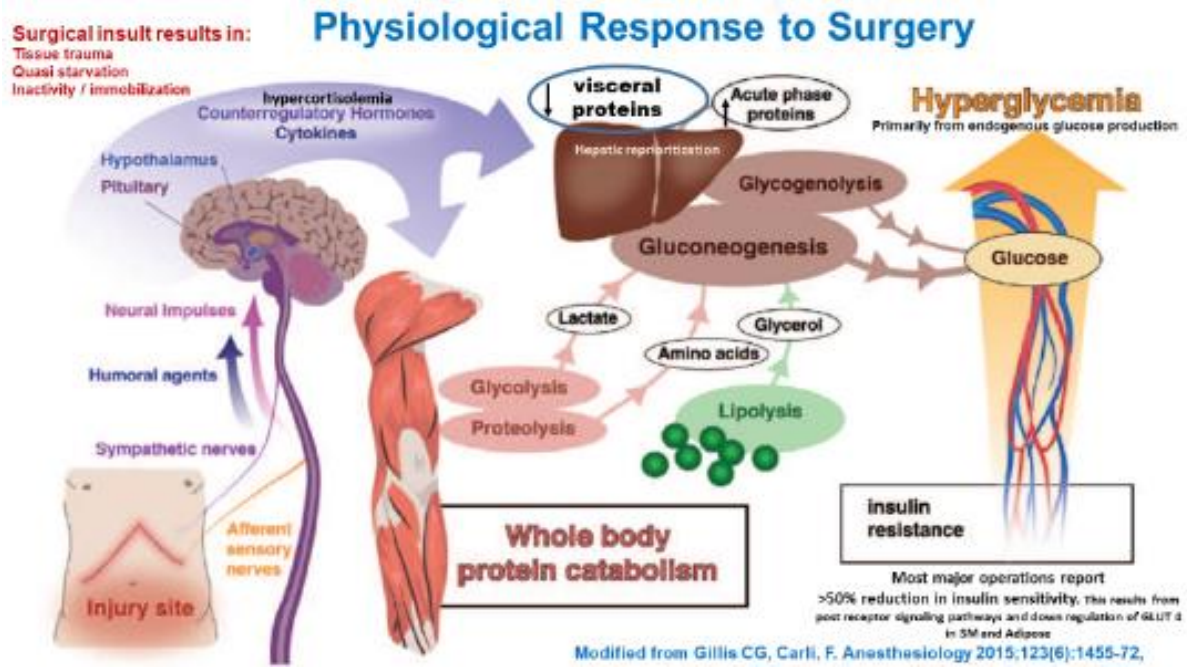
- **Timed stair climb**
  Reddy S et al JACS 2016

- **Increasing interest in "age-related" risk factor evaluation**
  - Functional status, sarcopenia, frailty, nutritional status, polypharmacy
  - Hamilton J JSR 2021, Holden TR Surg Endo 2022

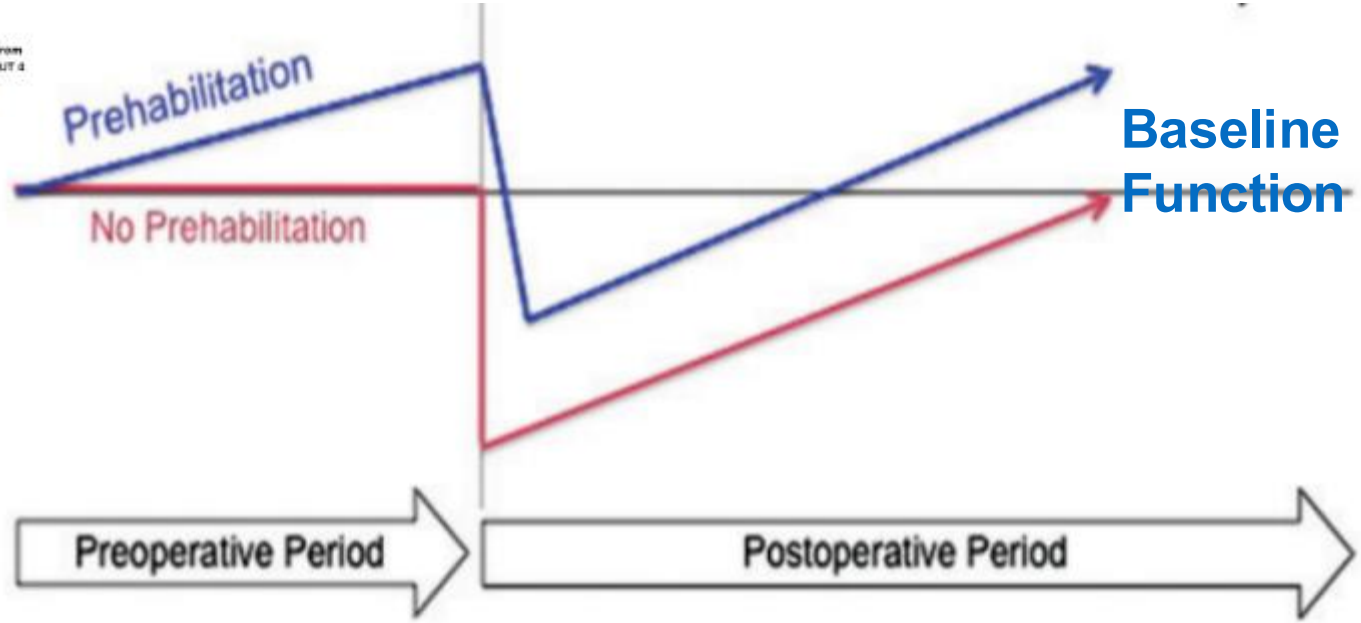
- **Specific Nutritional Risk indicators specifically in Orthopedic –mGNRI or OFRS**

Bottom Line for Ortho: BMI < 18.5 kg/m^2 ---- Unintentional weight loss last 6 months-----Albumin <3.5gm/dL

mGNRI – modified Geriatric Nutrition Risk Index



Prehabilitation Concept



Major surgical insult results in:

Systemic catabolic effects

- muscle loss

Tissue trauma

Quasi starvation

Inactivity / immobilization

- 50% reduction insulin sensitivity

Modified from Carli F. et al. Curr Opin Clin Nutr Metab Care. 2005; 8; 23-32

What is the data supporting prehabilitation prior to orthopedic surgery ?

Original Investigation | Orthopedics

Prehabilitation for Patients Undergoing Orthopedic Surgery
A Systematic Review and Meta-analysis

JAMA Network 2023

Anuj Punnoose, MSc; Leica S. Claydon-Mueller, PhD; Ori Weiss, MD; Jufen Zhang, PhD; Alison Rushton, EdD; Vikas Khanduja, PhD

UK Study: 48 RCTs met criteria with 3570 participants

- **CONCLUSIONS AND RELEVANCE**
- "In this systematic review and meta-analysis of RCTs, prehabilitation was associated with moderate improvement in several preoperative outcomes (function, knee flexor and hip abductor strength, HRQOL, 6-minute walk test) among patients undergoing all orthopedic procedures and was also associated with a reduction in back pain among patients undergoing lumbar surgery. However, the evidence was inconsistent and the quality of evidence for postoperative outcomes was low to very low. A **minimum duration of 4 to 6 weeks and 2 sessions per week** may be recommended for patients undergoing orthopedic surgery. Prehabilitation programs with a combination of supervised and unsupervised sessions can be safely administered with minimal risks. Additional RCTs with a low risk of bias investigating preoperative and postoperative outcomes for all orthopedic surgical procedures are required."

Finding suggest moderate benefits both preop and postop!

THR, TKR, Lumbar Surgery

What population seems to gain the most benefit from Prehabilitation ?

Major abdominal surgery:

Consistently positive outcomes

Cardiothoracic Surgery:

Reduced time to extubation, decrease pulmonary complications

Orthopedic and Spine Surgery:

Widely variable results: majority positive effect, case dependent, frailty significantly increases benefit

Systematic Review and Meta-Analysis

Prehabilitation in Patients at Risk of Poorer Outcomes Following Total Knee Arthroplasty: A Systematic Review

Karimijashni M et al Journal of Arthroplasty 2025

Motahareh Karimijashni PT, PhD [a b], Samantha Yoo PhD (c) [c], Keely Barnes MHK, PhD [a b d], Héloïse Lessard-Dostie MPA [a], Tim Ramsay PhD [b c], Stéphane Poitras PT, PhD [a]

The Effects of Structured Prehabilitation on Postoperative Outcomes Following Total Hip and Total Knee Arthroplasty: An Overview of Systematic Reviews and Meta-analyses of Randomized Controlled Trials

J Orthop Sports Phys Ther 2025

Joshua A J Keogh, Isabelle Keng, Dalraj S Dhillon, Yoan Bourgeault-Gagnon, Nicole Simunovic, Olufemi R Ayeni

Prehabilitation in Frail Surgical Patients: A Systematic Review

Maria Baimas-George[1] · Michael Watson[1] · Sharbel Elhage · Armida Parala-Metz[2] · Dionisios Vrochides[1] · Bradley R. Davis[3]

World Journal Surgery 2020

Optimizing the Preoperative Preparation of Sarcopenic Older People: The Role of Prehabilitation and Nutritional Supplementation before Knee Arthroplasty

Pegreffi F et al Nutrients 2023

Francesco Pegreffi [1,2], Rita Chiaramonte [3,4], Sabrina Donati Zeppa [5,*], Fulvio Lauretani [6,7], Marco Salvi [6,7], Irene Zucchini [6,7], Nicola Veronese [8], Michele Vecchio [4], Alessia Bartolacci [5], Vilberto Stocchi [9], Marcello Maggio [6,7]

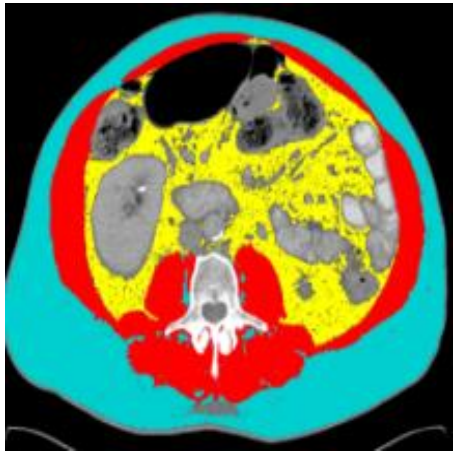
★ Excellent of literature nutritional supplements

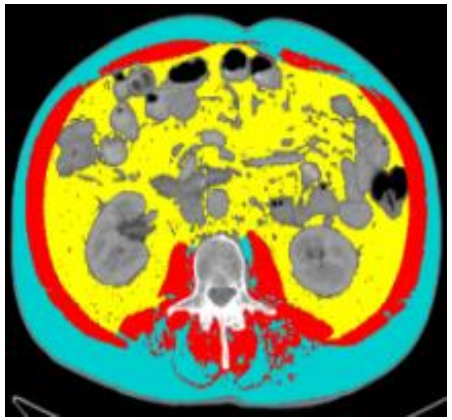
Body composition useful or is all this recent talk just “sarcomania”

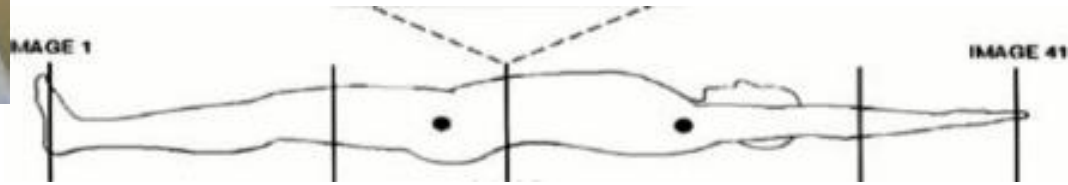
Diseases now proven to have correlated body composition to outcome:

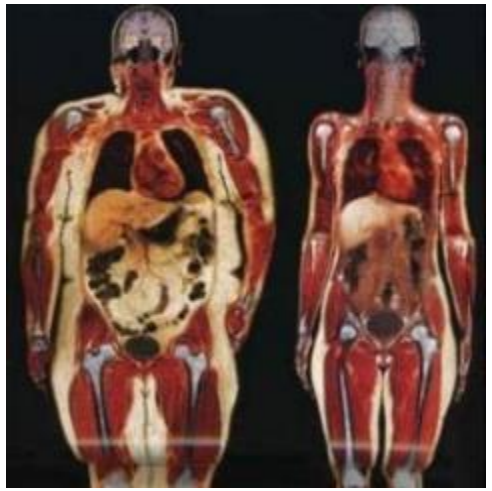
- Colorectal Cancer
- Pancreatic Cancer
- Esophageal Cancer
- Lymphoma
- Elderly trauma in ICU
- Hepatoma
- Lung Cancer
- AWR and Ventral Hernia
- Liver Transplant
- 30 d mortality in sepsis
- ECMO
- COVID
- Orthopedics (total joints, spine, hip fxs)
- etc?

Vicki Baracos









1. Peng P et al J GI Surgery 2012
2. Kirk PS et al J Surg Res 2015
3. Okumura S et al Surgery 2015
4. Mundi M et al Nutr Clin Practice 2019
5. Xiao J et al JAMA Surg 2020
6. Schlossse KA et al Am Surg 2019
7. Moisey LL et al CC 2013
8. Prado CM et al Ann Med 2018
9. Ji Y et al Jour Crit Care 2018
10. Bear D et al CCM 2021
11. van Rooijen MMJ WJS 2019
12. Jogiat UM et al Ann Surg 2023
13. Li L et al Scientific Reports 2025
14. Gaddikeri MB et al European Spine 2024
15. Witard OC et al Exp Physiology 2025

How much resistance exercise dose it take to make a difference? Physical activity and supplements

- N=100 nursing home residents (87 y)
- Placebo-controlled, randomized trial (FICSIT)
- Resistance training +/- supplements for 10 weeks
  - Hip and knee extension 3 x per week
  - Oral supplement 360 kcal/d
  - Combination physical activity and supplement
  - Placebo-group only received supplement

Fiatarone MA et al. N Engl J Med 1994;330:1769-1775

Physical Activity and Supplements – (Continued)

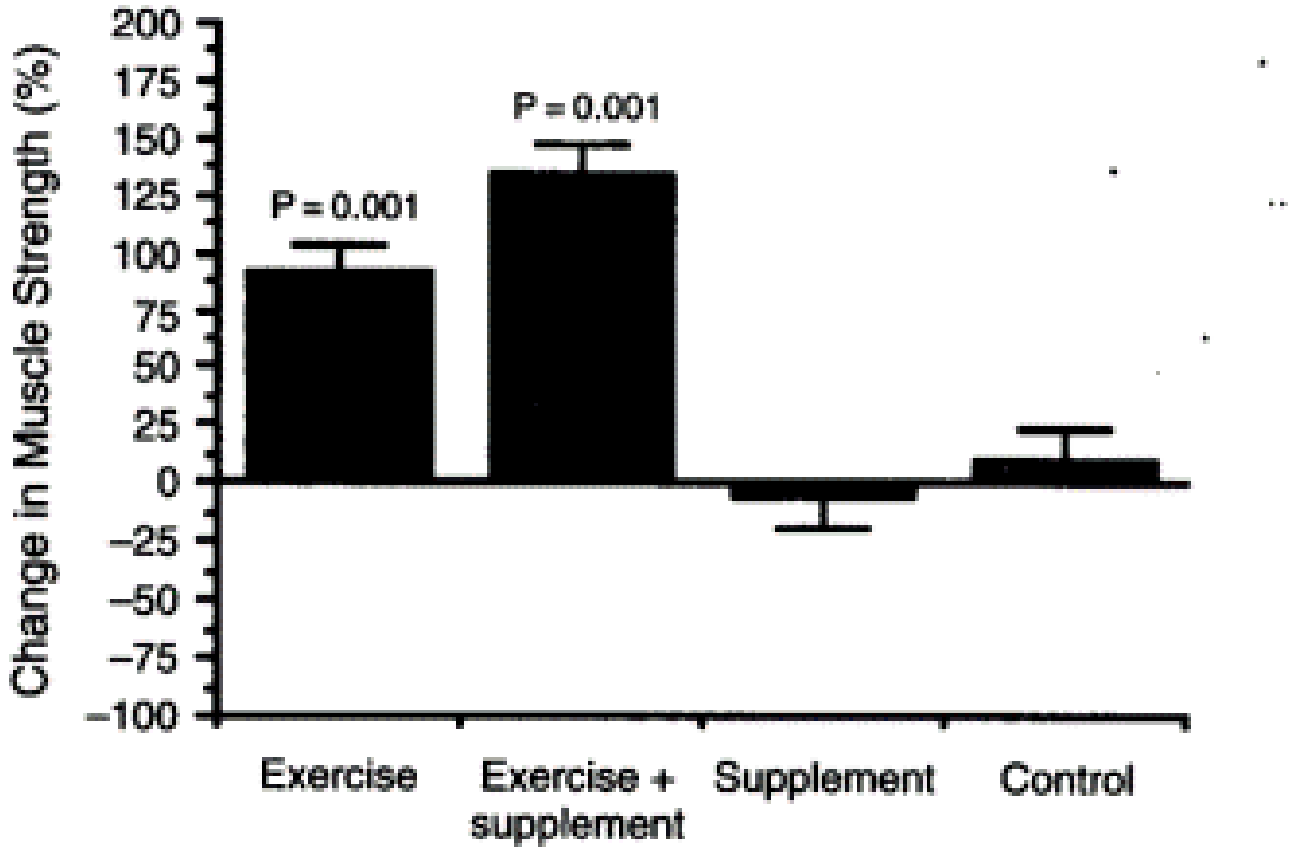
Fiatarone MA et al. N Engl J Med 1994;330:1769-1775

Strength:

- Resistance training: increase 113 (+/-8%)
- Placebo: increase 3 (+/-9%) (p<0.001)

Gait speed:

- Resistance training: increase 12 ±4%
- Placebo: decrease 1 ±4% (p=0.02)



Supplement:

- **Effect only noted when supplements combined with physical activity**

★ More recent references: --protein following exercise in muscle protein synthesis

Reidy PT et al J. Nutr 2013-
Leenders M et al J Gerontology 2013
Witard O et al Biogerontology 2016

Individualize program with patients ability

- 4 to 6 weeks before surgery:
  - Aerobic exercise
    - Walking, biking, swimming, mowing lawn
  - Strength training
    - Light weights (3-10lbs)
  - Balance exercise
    - Yoga, sit to stand, walking on line
- >30 min per day if possible
  - Continuous or broken up
  - Every day if possible
- Exercise at “moderate pace”
  - Be able to carry on conversation while exercising

Renshaw SM Surg 2021

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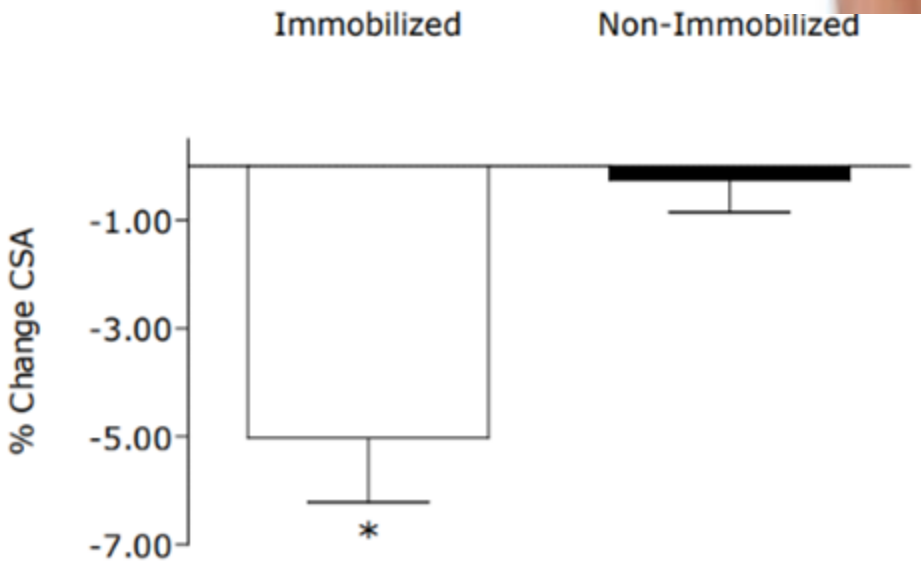
Can additional protein or amino acid supplements improve muscle mass in the perioperative period?

- Resistance exercise / early mobilization
  - Minimize neuromuscular blockage, wean from vent, sedation holidays

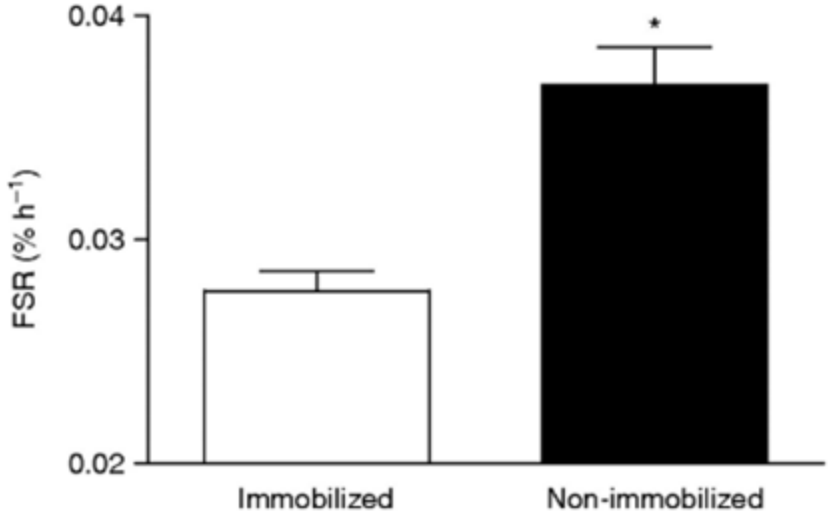
- Decrease systemic and intramuscular inflammation or increase inflammation resolution
  - Fish oils
  - Minimize loss of muscle satellite cells

- Specific fuels
  - Protein
  - Fish oils
  - MCT
  - SCFA
  - Carbohydrate
    - Avoiding hyperglycemia

Atrophy confined to the immobilized limb

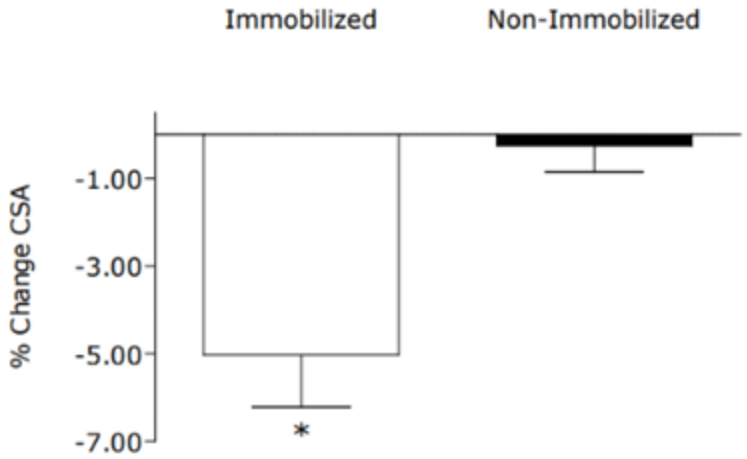


Resting fasted MPS (fractional synthetic rate: FSR)

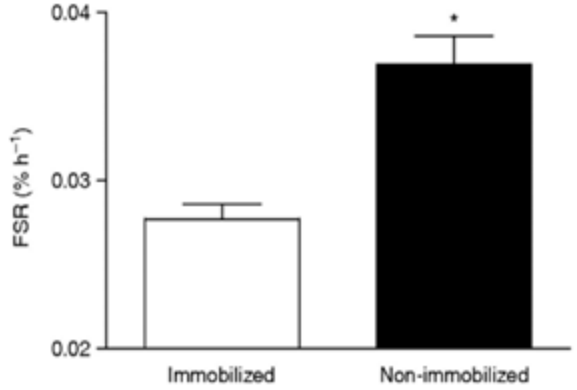


Glover E et al Journal Physiology 2008

Atrophy confined to the immobilized limb



Resting fasted MPS (fractional synthetic rate: FSR)

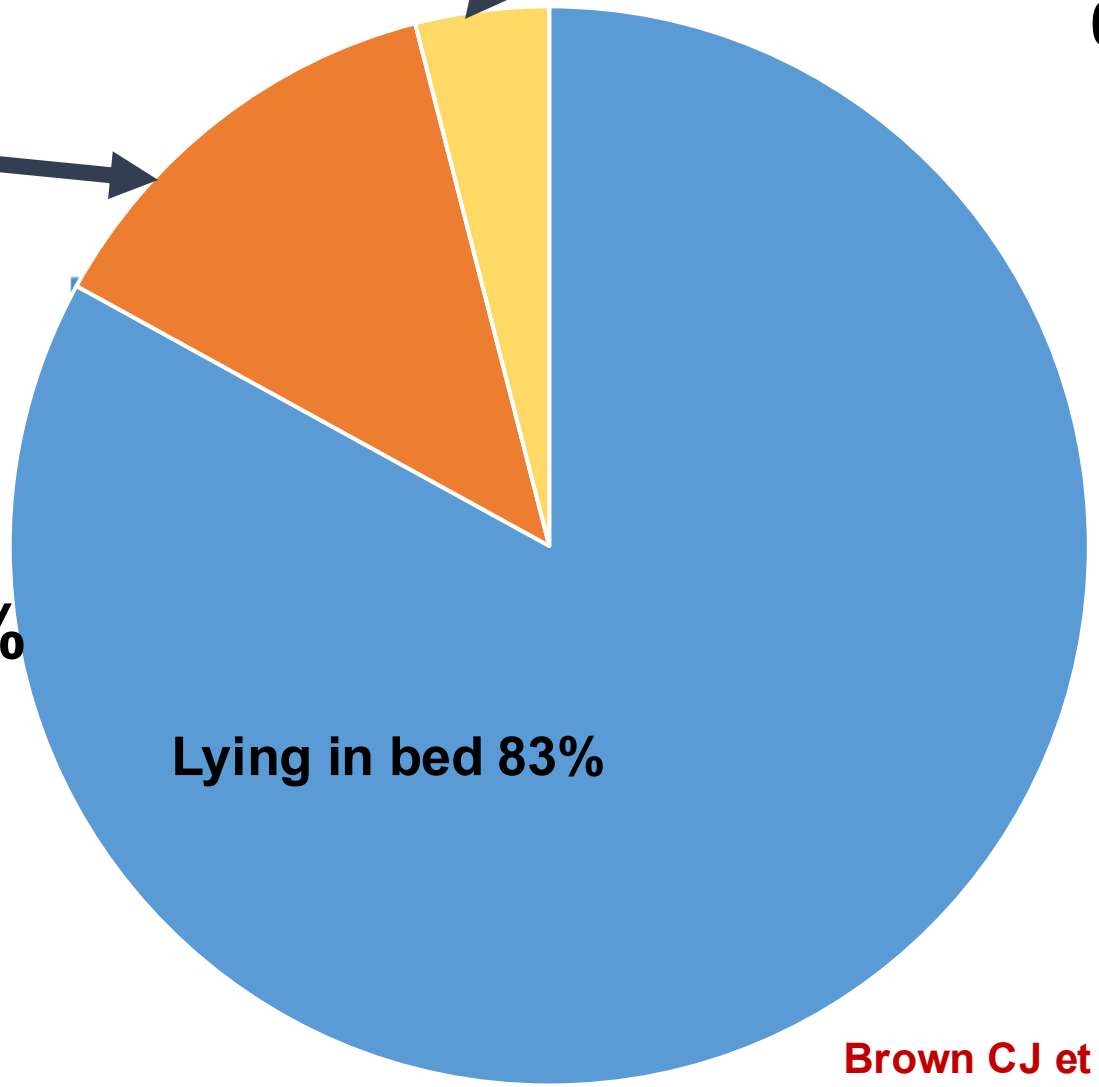


What is the mechanisms for this significant change?

1) physical inactivity decreases muscle sensitivity to anabolic property of dietary protein
2) muscle contraction stimulates protein synthesis (26%)
3) decrease in postprandial insulin sensitivity by 43%

Glover E et al Journal Physiology 2008

Activity while hospitalized



In healthy older adults when reducing step count by 76%, reduces postprandial insulin sensitivity decrease 43% and decreases post absorptive MPS by 26%

(Breen L et al J Clin Endo Metab 2013)

0.5 to 0.6% loss of protein per *day* in short term disuse studies

Muscle loss occurs at rate of 2% to 3% per day in catabolic and inflammatory states

Brown CJ et al Am Geriatric Soc 2009
Flower L et al JPEN 2022

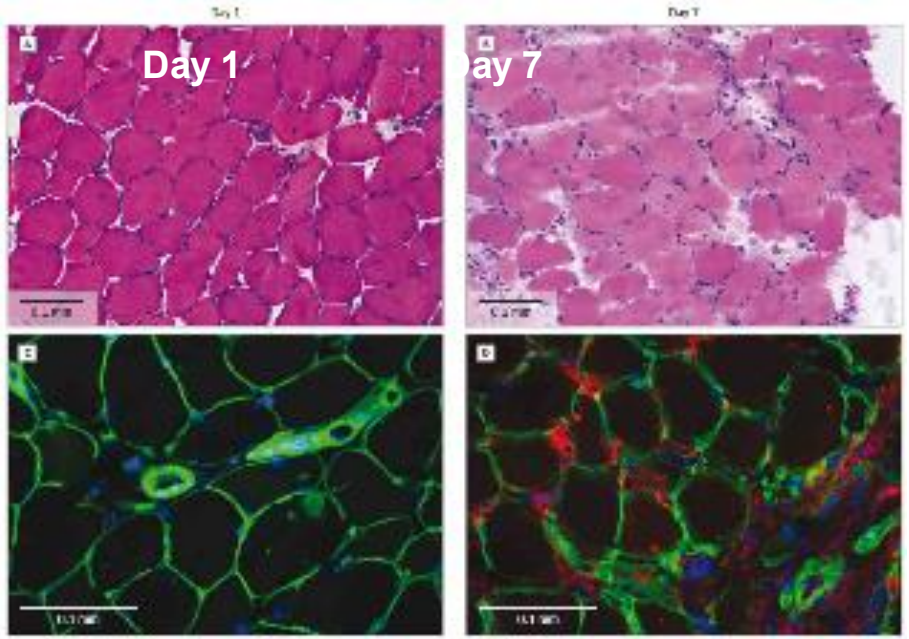
(MPS = Muscle protein synthesis)

Acute Skeletal Muscle Wasting in Critical Illness

Zudin Puthucheary

- Prospective study of 63 critically ill patients
  - Expected stay > 7 days, Vent > 48 hours
- 3 methods to determine muscle loss
  - Serial US
  - Histology
  - Biochemistry – DNA/Protein ration and fractional synthesis breakdown rates. (Leucine uptake etc)

- Conclusions
  - CSA of rectus femoris decrease 10% US
  - CSA of muscle fibers decrease 17.5%
  - Ratio protein to DNA decrease 29%
  - >40% of patients showed myofibril necrosis
    - Significant inflammatory changes in muscle noted
    - Loss of Satellite cells (personal communication)



- Muscle wasting occurred despite delivery of 0.7gm/kg protein

Puthucheary ZA et al JAMA 2013

Mechanistic data support increased infusion of AA's or protein increases net protein uptake in muscle

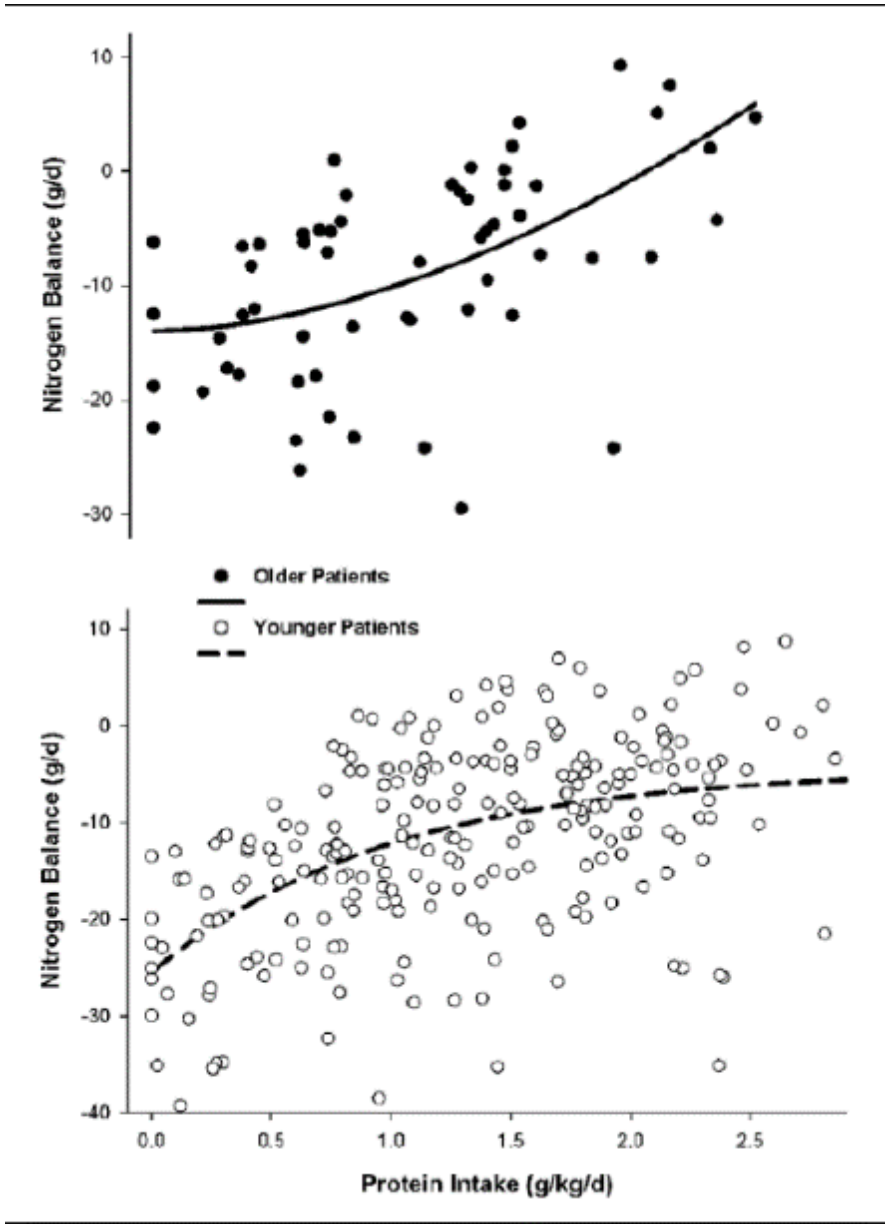
"Older" studies

Cuthberson - Shils M-- Cahill G--Cerra F--Vars S--Plank L--Cynober L -- Wolfe R

More recent studies using tracer technology

- **Weijs P et al 2014**
  - Protein goal beneficial, energy goal not an issue
- **Rooyackers O et al Clin Nutr 2015**
  - **WB protein synthesis – MOF**
  - Critically ill are able to utilize additional AA loads
- **Berg A et al Crit Care 2013**
  - **Protein kinetics hypocaloric vs normocaloric feeding**
  - increased protein = improved outcome
- **Liebau F et al Am J Clin Nutr 2015**
  - **Enteral protein WB protein turnover**
  - Additional protein beneficial
- **Zusman O et al Crit Care 2016**
  - Higher protein associated with improved mortality
- **Ferrie S JPEN 2016**
  - Increase AA infusion
  - Small improvements
- **Sandstrom-Rehal M et al Critical Care 2017**
  - Increase protein infusion increases synthesis in 24h infusion
- **Weijs P et al 2019**
  - N=801 Medical ICU pts
  - Increase protein increase survival 90d post d/c
- **Nakamura K et al 2021**
  - N=117 ICU patients high vs low protein
  - Higher protein yielded + muscle mass only if muscle stimulation
- **van Ruijven IM et al 2022**
  - N= 2618 mechanically ventilated ICU pts
  - Improved survival in pts getting > 1.2gm/kg/d (CRRT)
  - **No apparent benefit in sepsis**
- **Heyland DK et al ESPEN 2022**
  - Effort Trial = high vs lower protein
  - **No benefit** to high protein

Trauma Patients Nitrogen Balance: young vs old

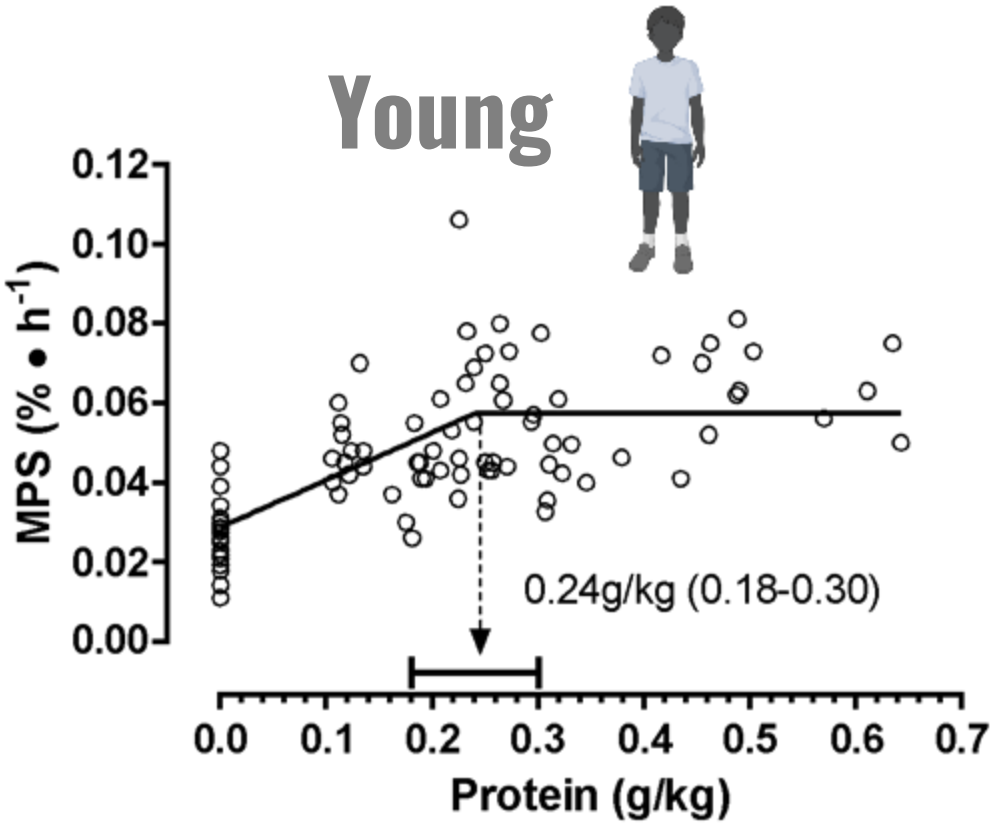


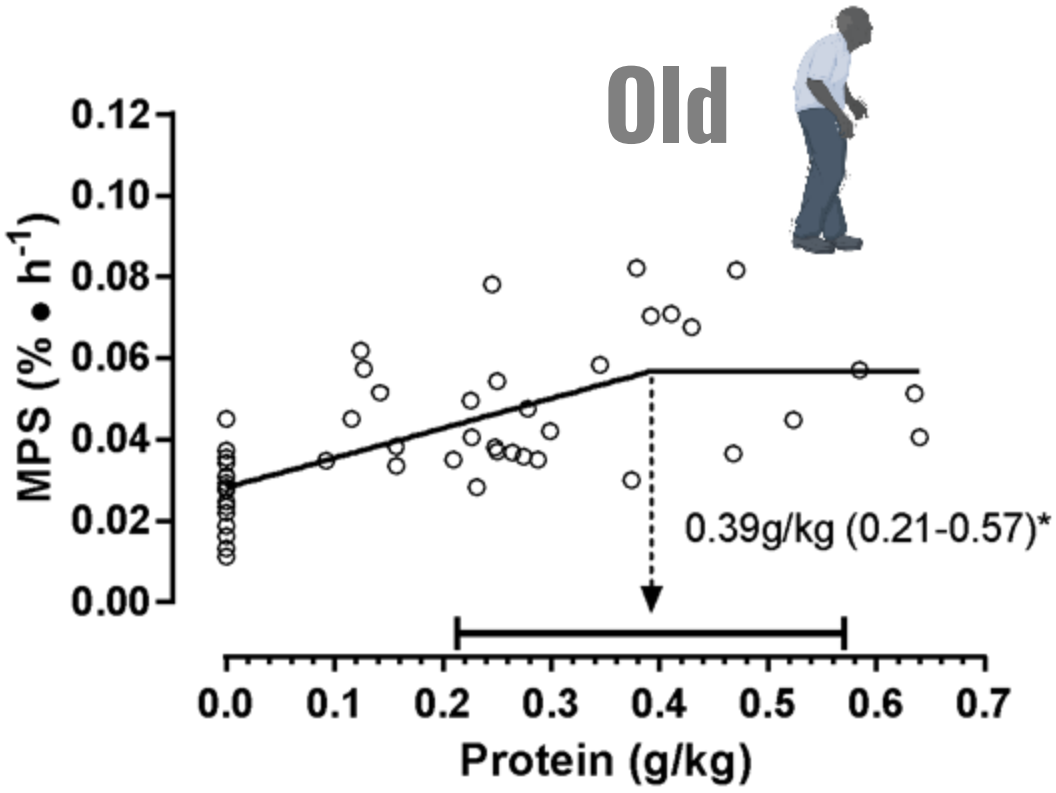
Note: a much higher protein level is required in > 65 yo before curve turns positive direction

Dickerson R et al JPEN 2015

Anabolic Resistance: higher protein and resistance exercise can partially overcome anabolic resistance: Increasing muscle force of contraction pre-op

➔ Elderly men require more protein to optimally stimulate muscle protein synthesis





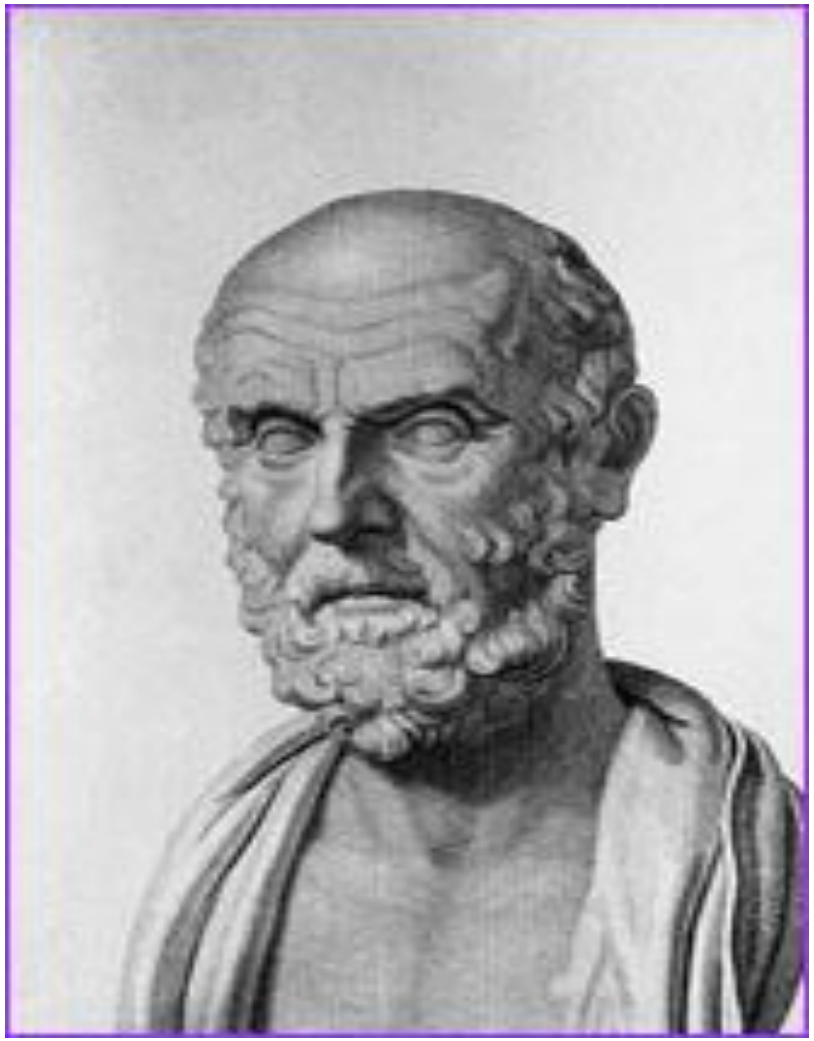
★ MPS = Muscle Protein Synthesis

Moore et al. *J. Gerontol. A Biol. Sci. Med. Sci.* 70(1): 57-62, 2015

Can metabolic manipulation improve outcome ?

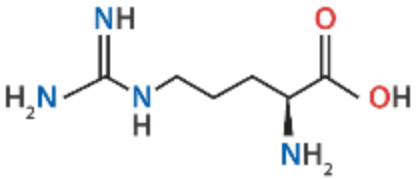
- **"….fever and inflammation can be considered as healing processes, if restrained with in certain limits, but as a process which might be harmful if those limits were exceeded….."**

- **Hippocrates**

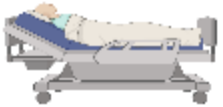


What about metabolic modulating formulations in surgery ?

Arginine



- Improved protein kinetics
- Improved wound healing
- Restores T cell function
- M1 to M2 macrophage conversion
- Aids in MDSC maturation
- Clinical outcomes
  - Decrease infection
  - Decrease LOS

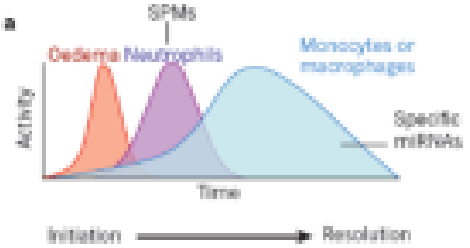


RNA

- T cell regulation
- Increase pathogen clearance
- Purinergic signaling
  - Visceral blood supply regulation

Fish oils

- Attenuates metabolic response to stress
- Decreases loss of muscle with immobilization
- Decreases:
  - Inflammation
  - TLR4 receptor binding
  - ICAM-1 expression
  - NFkB
- Increases:
  - SPM's
    - Stimulates resolution of inflammation
      - M1 to M2 conversion
    - Enhance WBC function
    - Decrease post op pain
    - Increase tissue regeneration
  - Enhance diaphragm function
  - Bowel motility via vagal mx



Zhu X et al Ann Surg 2013
MacLeod AS et al Adv Wounds 2015
McCarthy M, Martindale R Nutrition Clin Prac 2018

Serhan C Nature 2014
Dalli J et al J Immunology 2016
Serhan C et al JCI 2018
Chiang CN Essays in Biochem 2020

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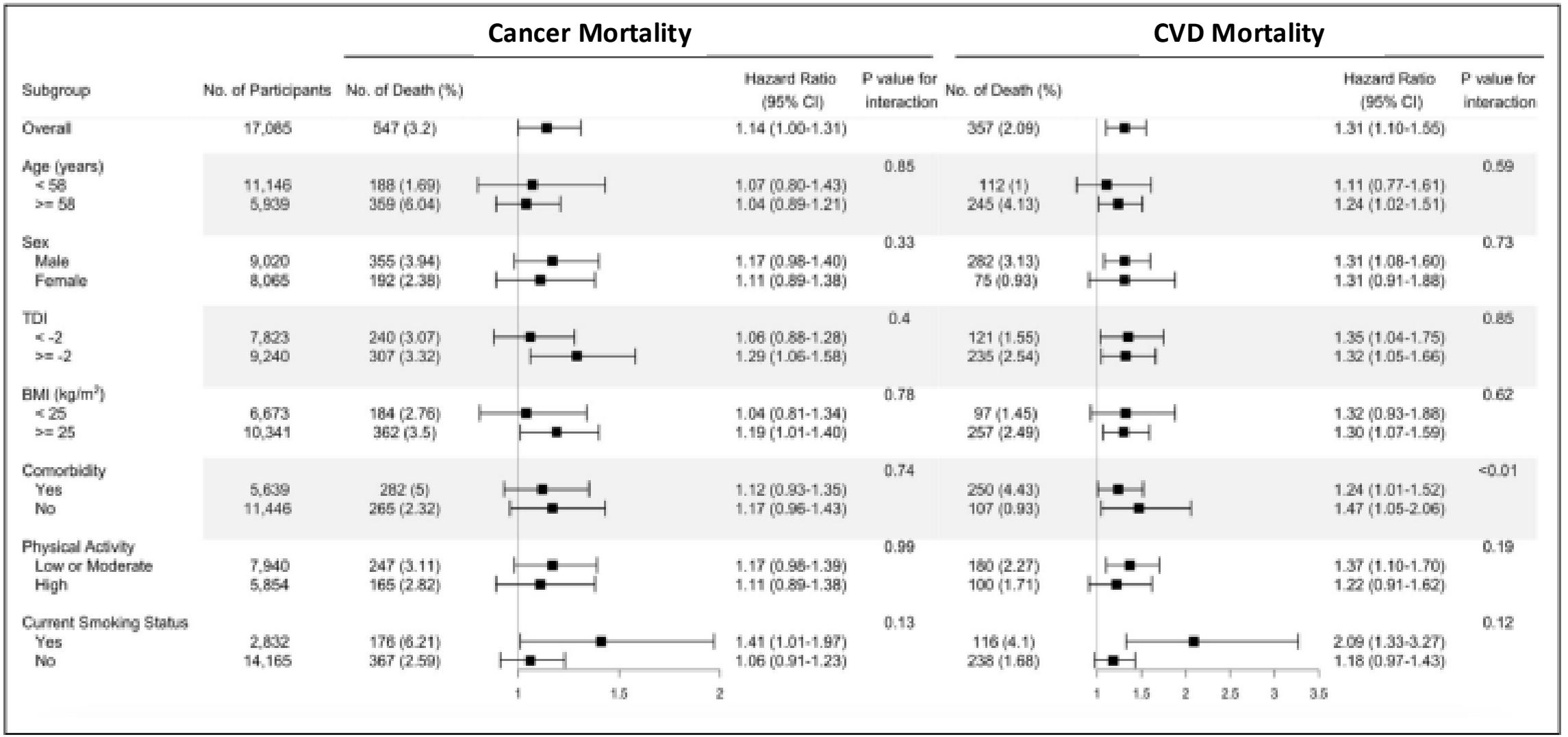
Omega 6 to Omega 3 Ratio and All Cause Mortality



UK Biobank Study

502,384 subjects with 85,425 subjects with complete data on PUFA followed for 4 years (2006 to 2010)

14% decrease Cancer mortality and 31% cardiac mortality --- 26% decrease in all cause mortality

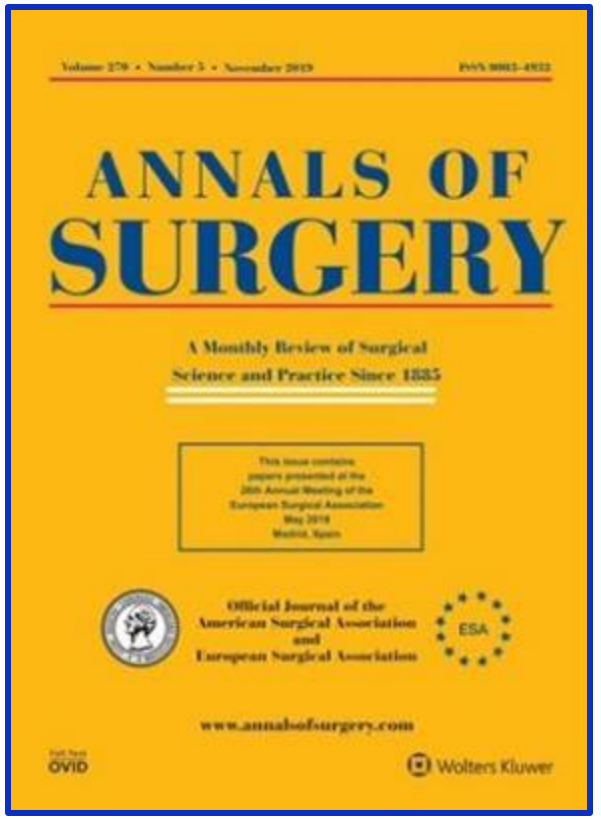
Zhang Y et al eLife 2023

Metabolic manipulation improving outcome ?

The Impact of Preoperative Immune Modulating Nutrition on Outcomes in Patients Undergoing Surgery for Gastrointestinal Cancer

A Systematic Review and Meta-analysis

Alfred Adiamah, MRCS, Pavel Skořepa, MD,*† Arved Weimann, MD, MA,‡ and Dileep N. Lobo, MS, DM, FRCS, FACS, FRCPE*§*



Ann Surg 2019

- 16 studies with strict criteria of study quality
- Study reviewed **ONLY** pre-operative cases
- Decrease in:
  - Infections
  - Length of hospital stay
  - Non-significant change in mortality
    - (+ signal but not quite positive)

Perioperative Immunonutrition in Elderly Patients Undergoing Total Hip and Knee Arthroplasty: Impact on Postoperative Outcomes Goncalves TJM et al JPEN 2021

Immunonutrition in Orthopedic and Traumatic Patients Nutrients 2023

by Pietro Gregori [1], Edoardo Franceschetti [1], Susanna Basciani [1], Lorenzo Impieri [2], Biagio Zampogna [1], Alfredo Matano [3], Carlo Manzi [4], Ludovico Carbone [5], Luigi Marano [5,*] and Rocco Papalia [1]

Multimodal perioperative care plus immunonutrition versus traditional care in total hip arthroplasty: a randomized pilot study Nutrition J 2015

Miguel Aprelino Alito[1] and José Eduardo de Aguilar-Nascimento[2,3,4*]

P3. Perioperative immunonutrition in spine and total joint surgery

Michael Shumaker DO [1], Bryan P. Hooks DO [1], Dhanunjay S. Boyalakuntla PhD [2], Matt S. Bishop CRNP [3]

The Spine Journal 2019

Improved outcomes with perioperative dietitian-led interventions in patients undergoing total joint arthroplasty: A systematic review Journal of Orthopaedics 2024

Steven L. Yee [a], R. Cole Schmidt [b], James Satalich [b], John Krumme [c], Gregory J. Golladay [b], Nirav K. Patel [d]

Widely studied including Ortho and Spine

Relative Range of Inflammatory Effects from Different Lipid Sources

Relative inflammation scale

Proinflammatory

Less inflammatory

Anti-inflammatory

Safflower oil

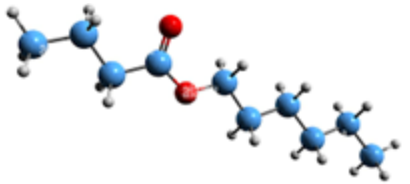
Soybean oil

Medium chain triglyceride oil

Olive oil

Fish oil

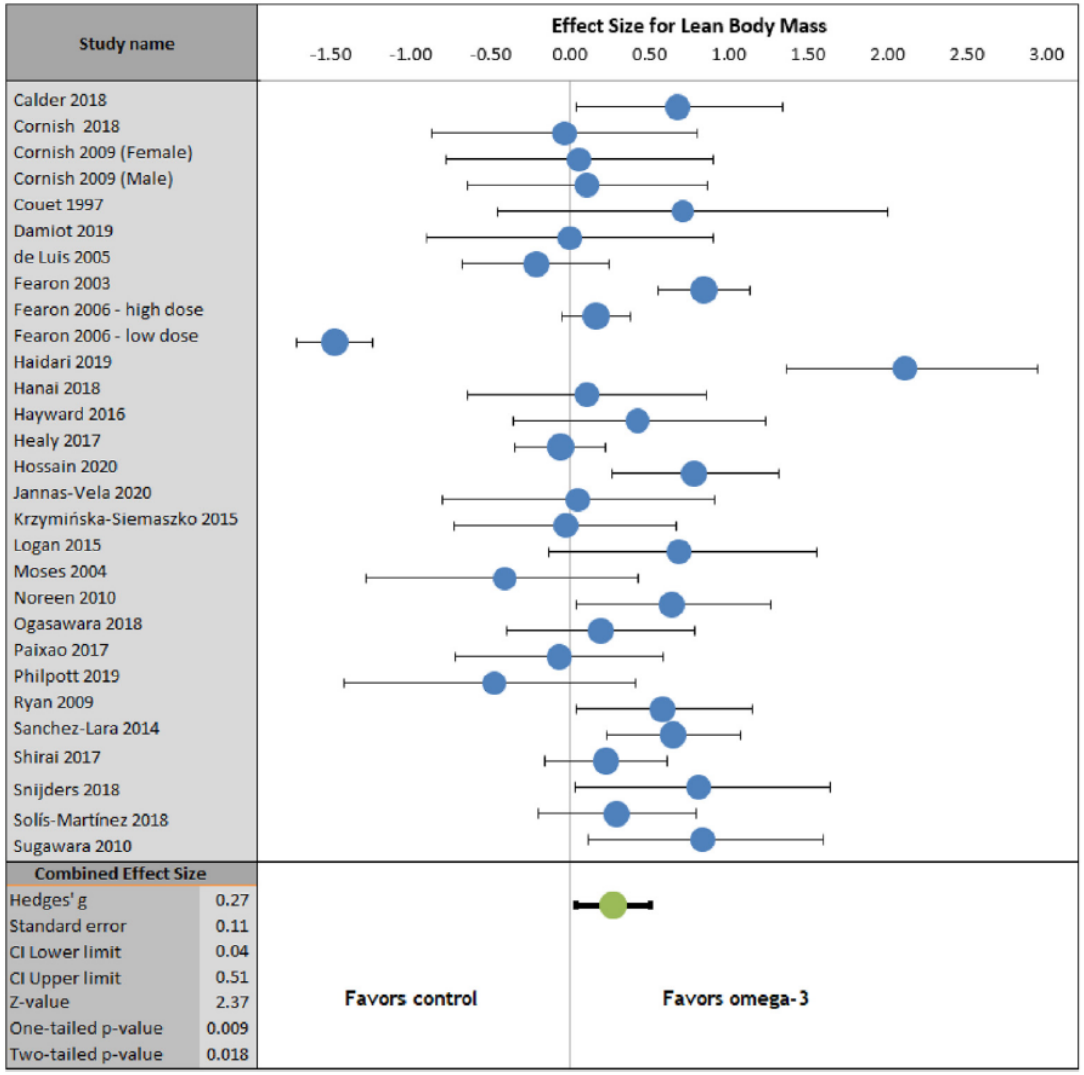
SCFA (Butyrate)



SPM's
Inflammation Resolution

Calder PC et al JPEN 2020
Martindale RG et al JPEN 2020
Vanek VW et al Nutr Clin Pract 2012

RCTs show omega-3s promote lean mass and muscle mass

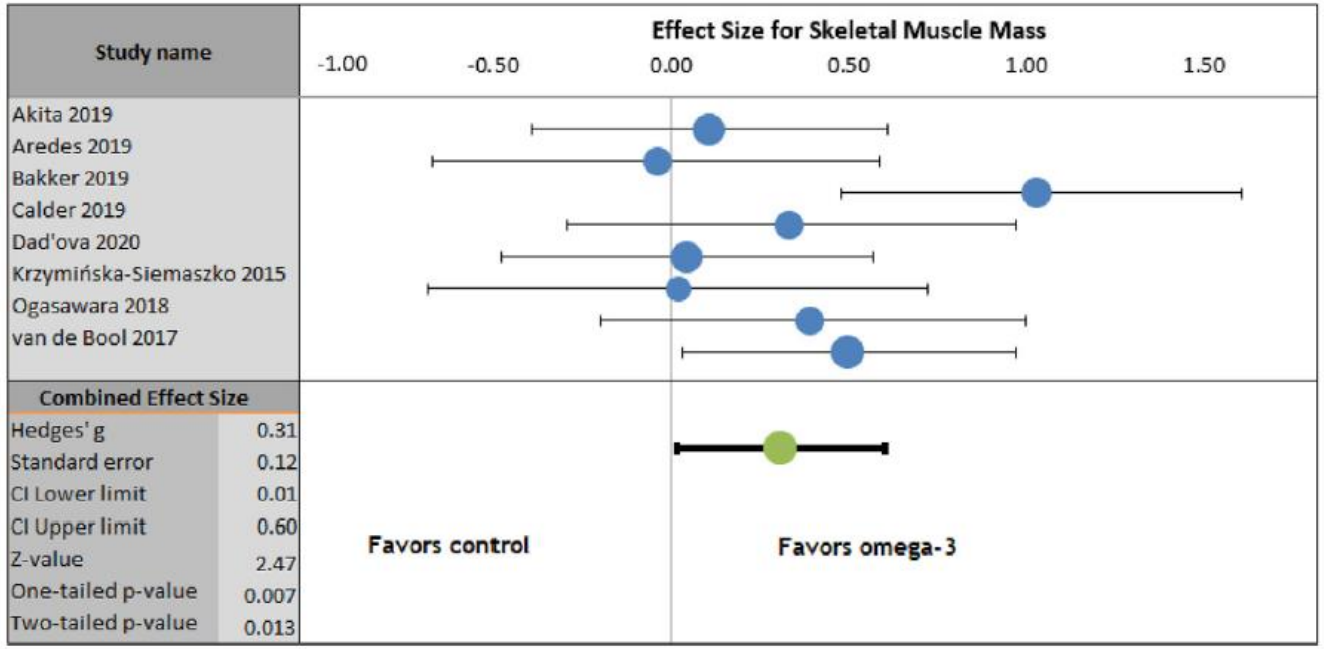


Meta-analysis

The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: A scoping systematic review and meta-analysis

Julia K. Bird [a], Barbara Troesch [b, *], Ines Warnke [c], Philip C. Calder [d, e]

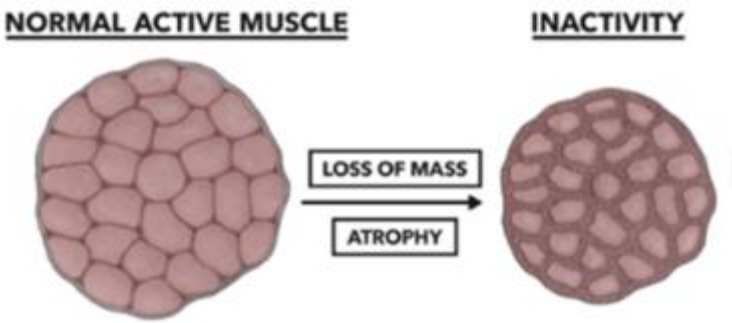
Bird JK et al Clin Nutrition 2021

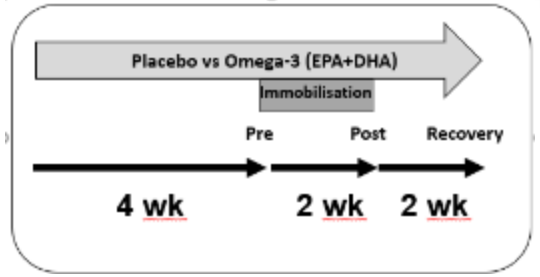


Omega-3 fatty acid supplementation attenuates skeletal muscle disuse atrophy during two weeks of unilateral leg immobilization in healthy young women

Chris McGlory,*,[1] Stefan H. M. Gorissen,* Michael Kamal,* Ravninder Bahniwal,* Amy J. Hector,* Steven K. Baker,† Adrian Chabowski,‡ and Stuart M. Phillips*

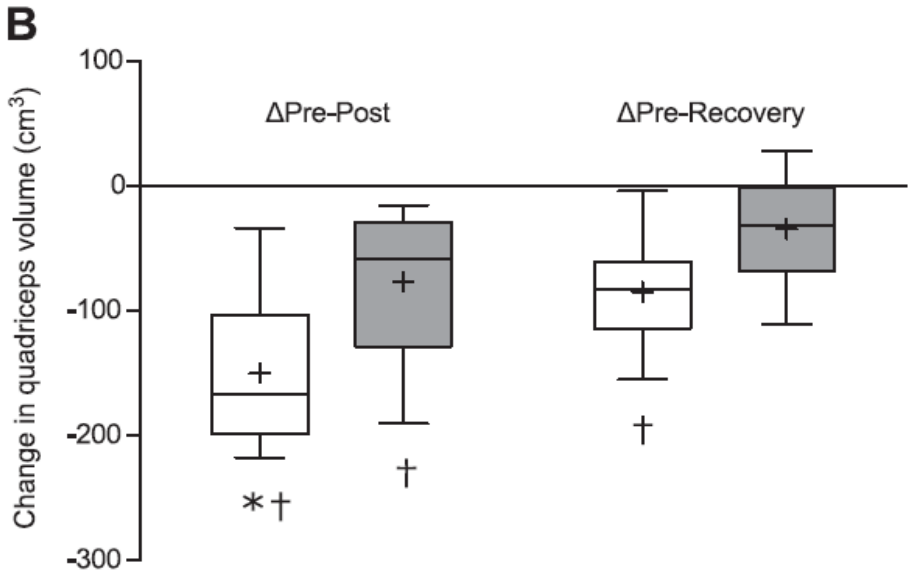
*Department of Kinesiology and †Division of Physical Medicine and Rehabilitation, Department of Medicine, McMaster University, Ham Ontario, Canada; and ‡Department of Physiology, Medical University of Bialystok, Bialystok, Poland



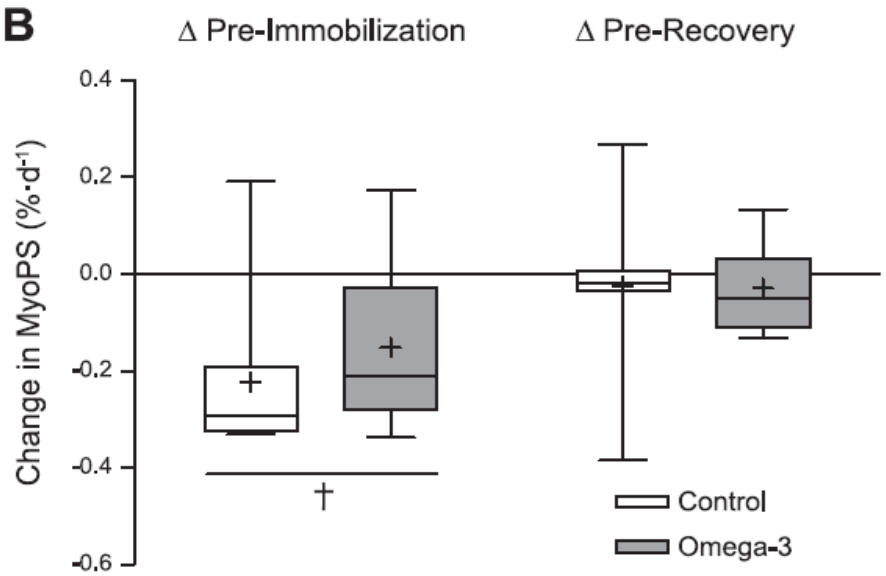


2.97 gm EPA + 2.03 gm DHA per day 8 weeks (5gm EPA/DHA)

Omega-3 group lost less muscle (quadriceps) during immobilization

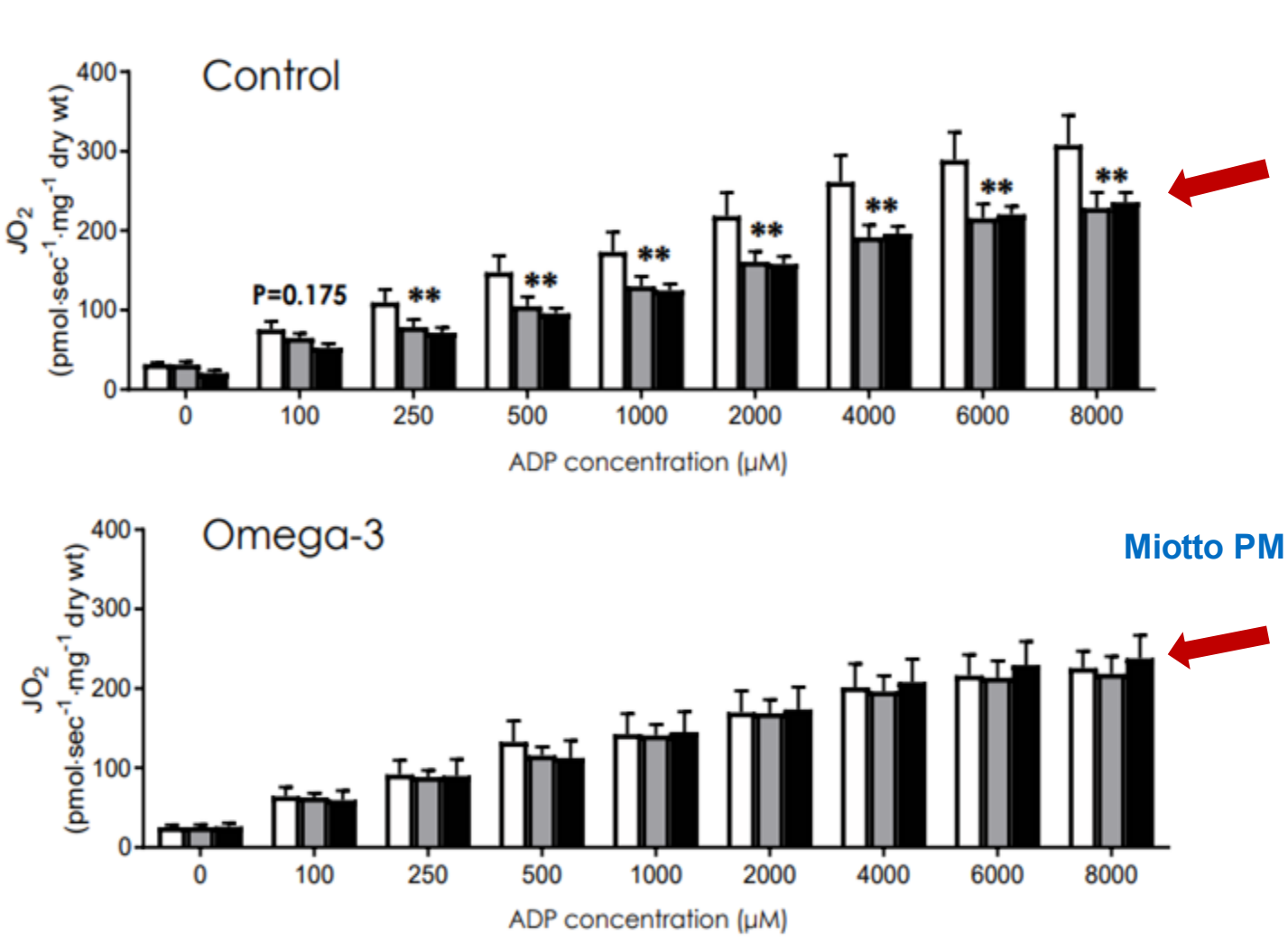


Omega-3 group improved muscle protein synthesis during immobilization was higher with omega-3s



McGlory C et al. (2019) FASEB J 33, 4586-4597

Omega-3 fatty acids protect against declines in mitochondrial respiration



P Miotto

Miotto PM et al FASEB J 2019

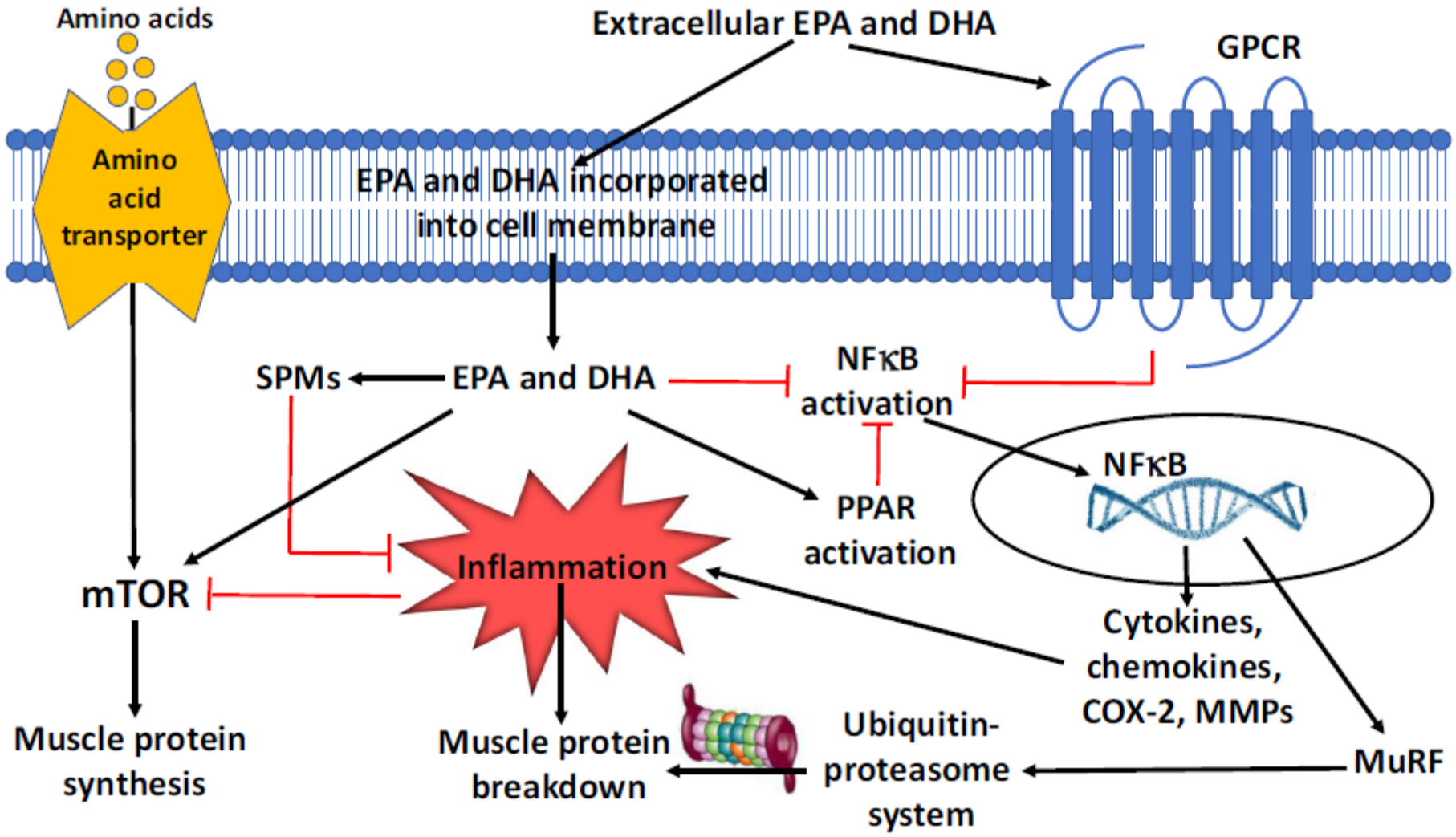
Note: no decrease in mitochondrial respiration in Omega 3 FA group

★ **4 wk 5 gm FO supplement pre immobilization and 2 weeks during immobilization**

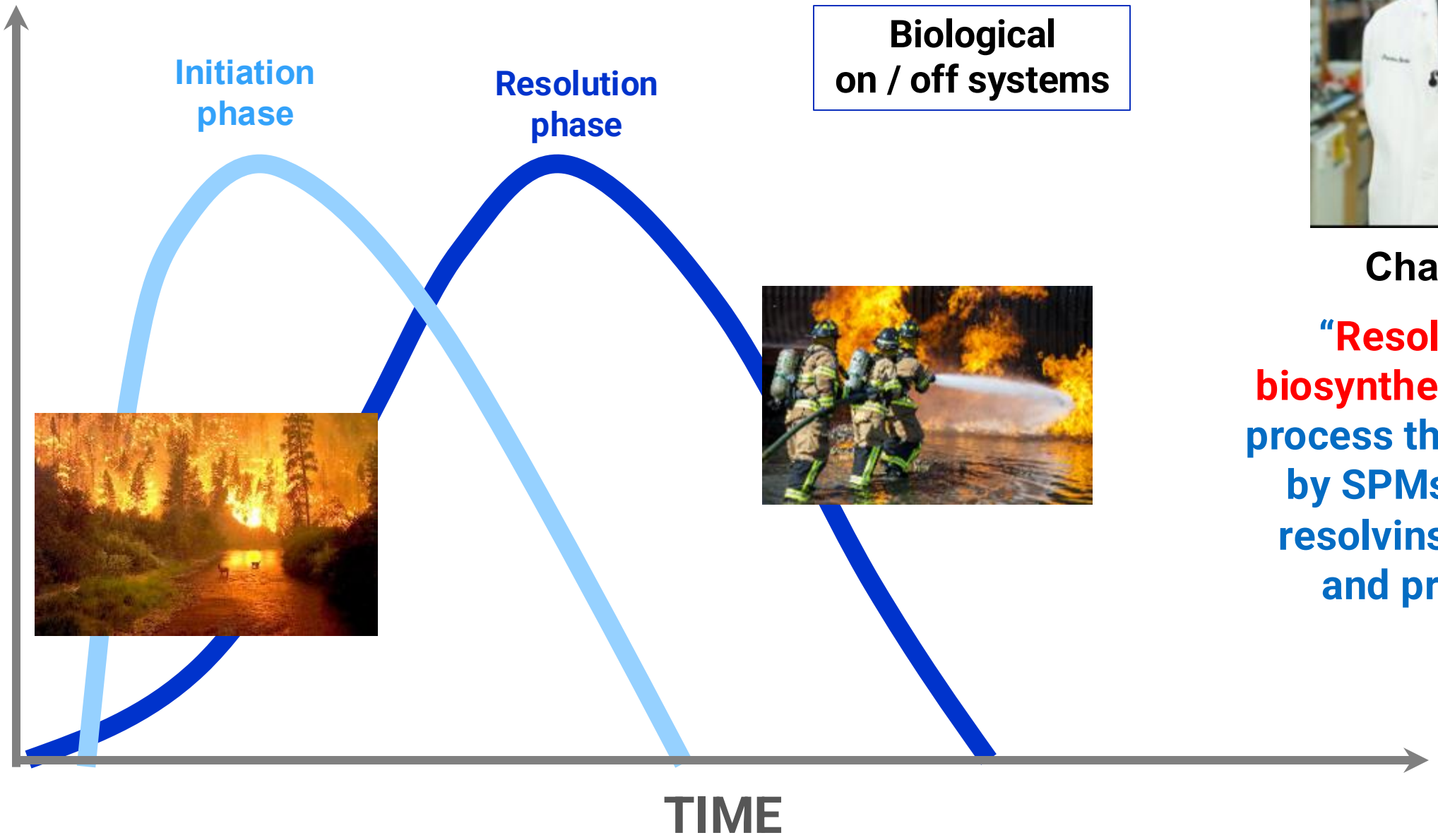
Combining proteins with n-3 PUFAs (EPA + DHA) and their inflammation pro-resolution mediators for preservation of skeletal muscle mass

Critical Care 2024

Renée Blaauw[1], Philip C. Calder[2,3], Robert G. Martindale[4] and Mette M. Berger[5*]



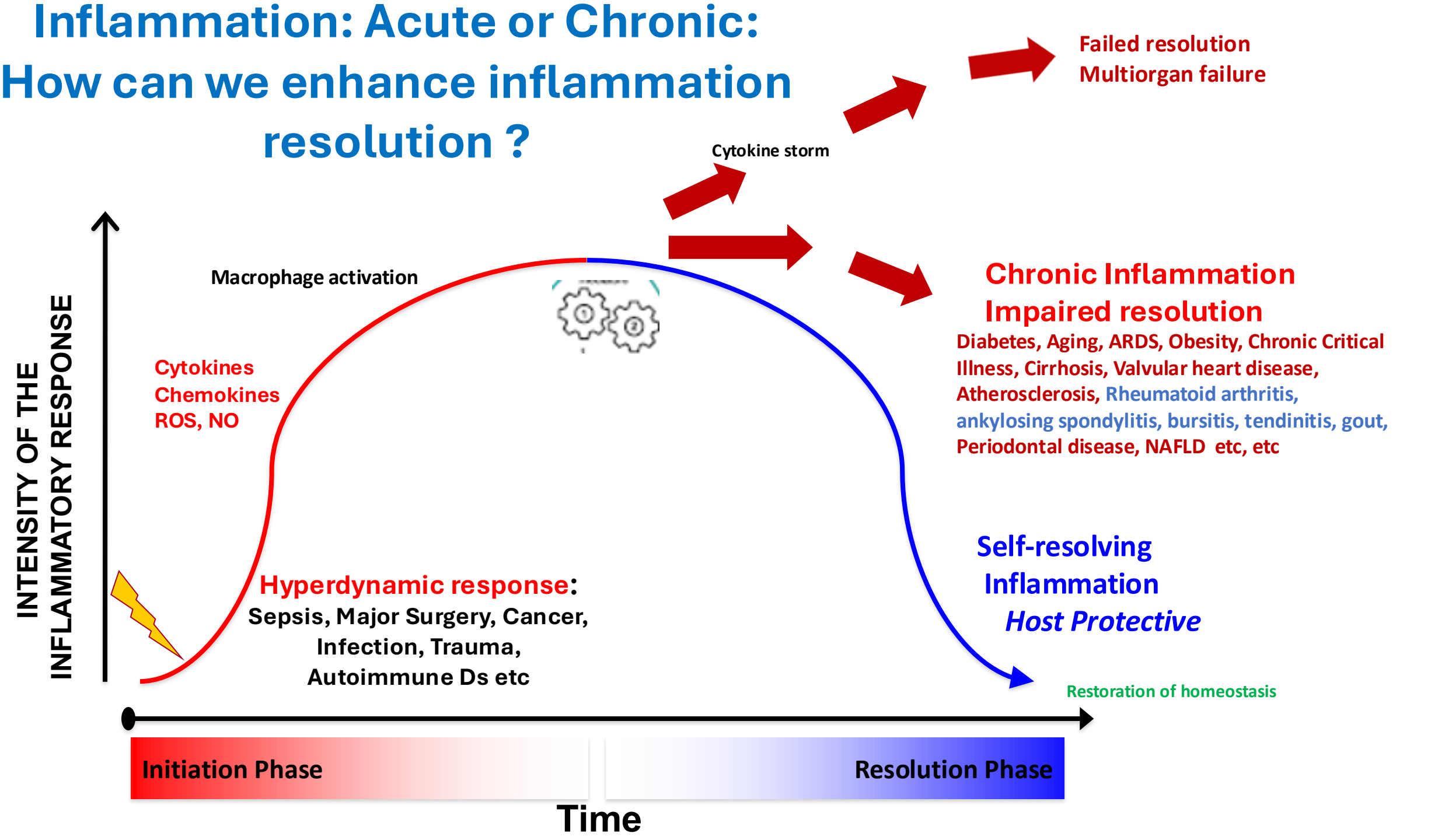
Inflammation has two phases: initiation and resolution



Charlie Serhan

"Resolution is a biosynthetically active process that is initiated by SPMs, including resolvins, maresins, and protectins"

Inflammation: Acute or Chronic: How can we enhance inflammation resolution ?



Tissue injury: Surgery, Cancer, Infection, trauma

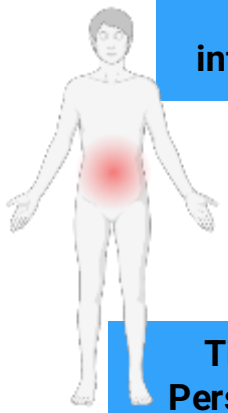
Acute inflammation

Resolvins, Protectins Maresins (SPMs)

SPM's

Chronic inflammation

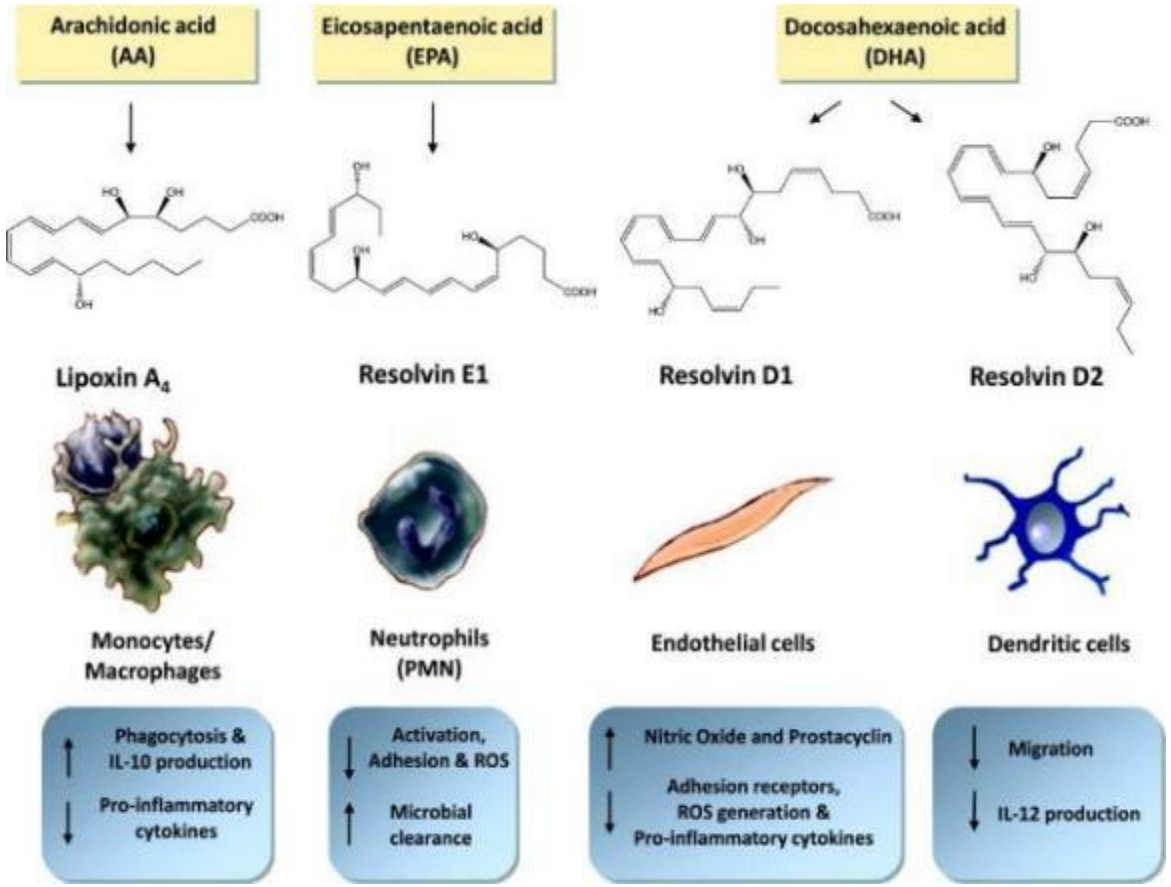
Inflammation Resolution



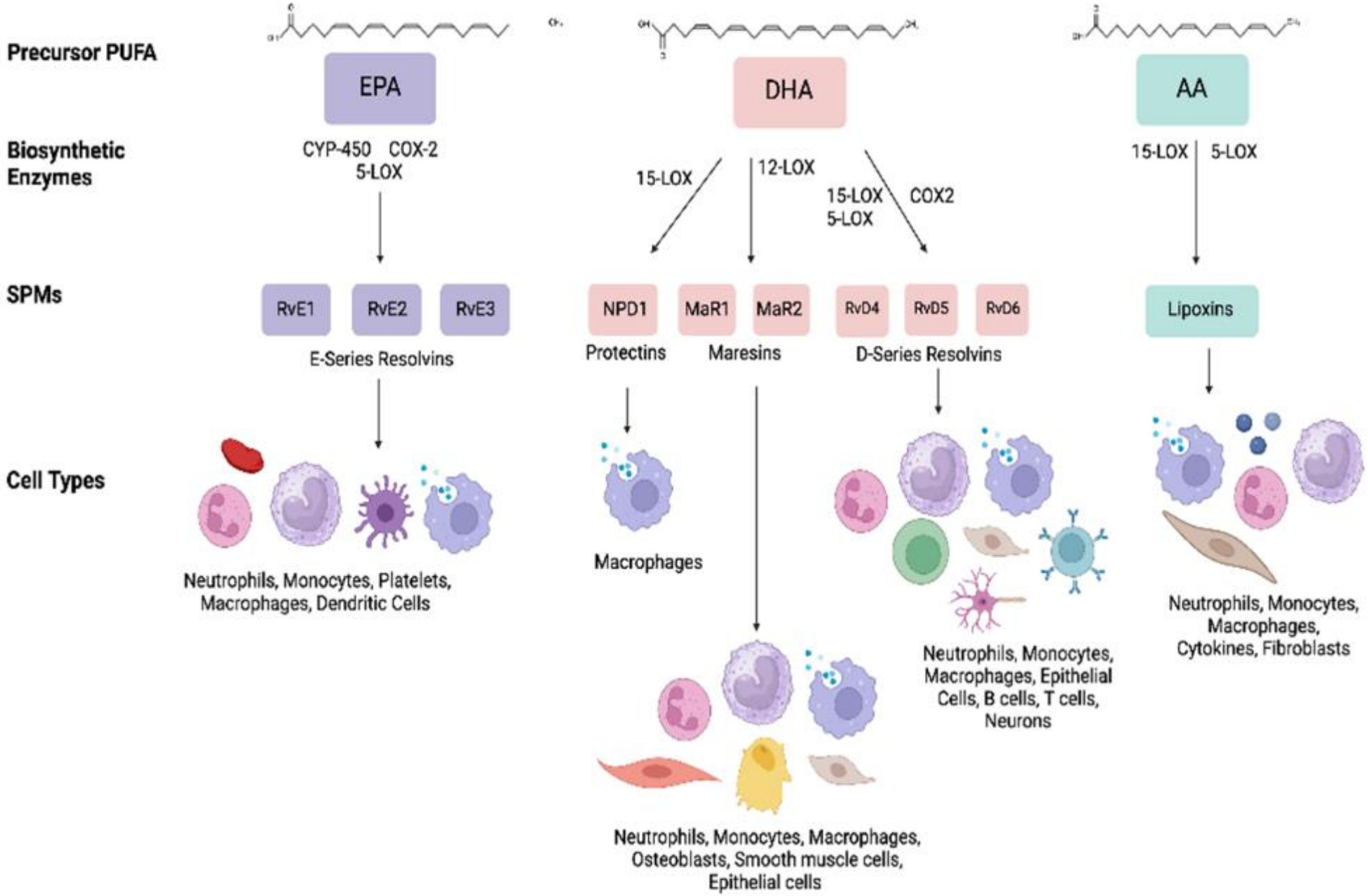
Tissue damage Persistent infection Autoimmune disease

Tissue repair, Healing

Serhan CN, Levy BD. J Clinical Investigations 2018

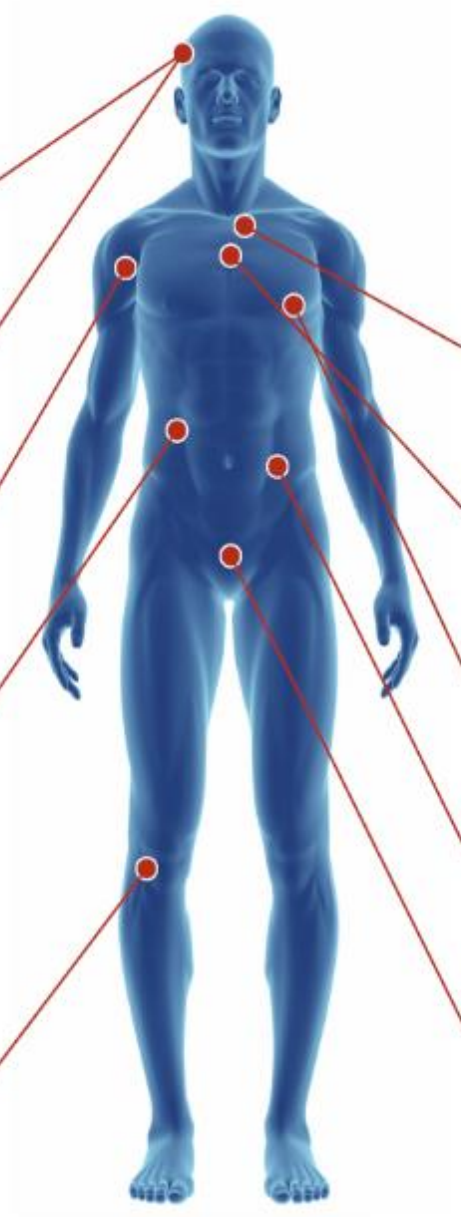


Created with BioRender.com



Gold S, Martindale R Current GI Reports 2025

Identification of SPM at Bioactive Levels in Humans



Brain
380-1800 pg/mg protein
Lukiv et al., 2005; Wang et al., 2015; Zhu et al., 2015

Cerebrospinal Fluid
11-390 pM
Pruss et al., 2013

Lymph Nodes
3-112 pg/100 mg
Colas et al., 2014

Adipose Tissues
2-3 pg/106 cells
Clària et al., 2012

Placenta
1-8 pg/mg
Keelan et al., 2015

Synovial Fluid
0.2-0.7 nM
Giera et al., 2012

Exhaled Breath Condensate
6 nM
Levy et al., 2007

Sputum (Cystic Fibrosis)
17-365 pg/mg protein
Yang et al. 2012

Plasma
3-30 pM
Colas et al., 2014; Mas et al., 2012; Arita et al., 2005

Serum
14 pM-6 nM
Colas et al., 2014; Mas et al., 2012; Psychogios et al., 2011

Breast Milk
10 pM-27 nM
Weiss et al., 2013; Arnardottir et al., 2016

Spleen
1-112 pg/100 mg
Colas et al., 2014

Urine
12-330 pM
Sasaki et al., 2015

SPMs are *not* in the diet, they are produced in-vivo from fish oil substrates, primarily DHA and EPA

Full benefits seen with extremely small amounts 10^{-9} to 10^{-12}

SPMs are evolutionarily conserved

Serhan CN Molecular Aspects of Medicine 2017
Chiang N et al Essays in Biochemistry 2020
Serhan CN et al Seminars in Immunology 2022

SPM = specialized pro-resolving mediator; EPA = eicosapentaeoic acid, DHA = docosahexaenoic acid

Resolvin D1 supports skeletal myofiber regeneration via actions on myeloid and muscle stem cells

James F. Markworth,[1,2] Lemuel A. Brown,[1] Eunice Lim,[1] Carolyn Floyd,[1] Jacqueline Larouche,[3] Jesus A. Castor-Macias,[3] Kristoffer B. Sugg,[2,4] Dylan C. Sarver,[2,5] Peter C.D. Macpherson,[1] Carol Davis,[1] Carlos A. Aguilar,[3] Krishna Rao Maddipati,[6] and Susan V. Brooks[1,3]

Daily systemic administration of the SPM RvD1 as an immunoresolvent limited the degree and duration of inflammation, enhanced regenerating myofiber growth, and improved recovery of muscle strength

RvD1: suppressed inflammatory cytokine expression
enhanced polymorphonuclear cell clearance
modulated the local muscle stem cell response
polarized intramuscular macrophages to a more proregenerative subset

SPMs active in modulating:
infiltrating myeloid cells
resident muscle cell populations

SPMs represent a novel alternative to classical anti-inflammatory interventions in the management of muscle injuries to modulate inflammation while stimulating tissue repair.

Markworth JF et al JCI Insight 2020

Muscle regeneration

Muscle injury models of traumatic or surgical loss of skeletal muscle leads to chronic inflammation and fibrosis

- Macrophage and neutrophil infiltration
  - Macrophages are critical regulators of tissue repair – lack of polarization to M2
- Lack of M1 transition to M2 leads to limited regeneration

Resolvin D1 supports skeletal myofiber regeneration via actions on myeloid and muscle stem cells

JCI Insight 2020

James F. Markworth,[1,2] Lemuel A. Brown,[1] Eunice Lim,[1] Carolyn Floyd,[1] Jacqueline Larouche,[3] Jesus A. Castor-Macias,[3] Kristoffer B. Sugg,[2,4] Dylan C. Sarver,[2,5] Peter C.D. Macpherson,[1] Carol Davis,[1] Carlos A. Aguilar,[3] Krishna Rao Maddipati,[6] and Susan V. Brooks[1,3]

Maresin 1 Repletion Improves Muscle Regeneration After Volumetric Muscle Loss

Jesus A. Castor-Macias[1,2,7], Jacqueline A. Larouche[1,2,7], Emily C. Wallace[1], Bonnie D. Spence[1], Alec Eames[1], Benjamin A. Yang[1,2], Carol Davis[3], Susan V. Brooks[1,3], Krishna Rao Maddipati[4], James F. Markworth[5], Carlos A. Aguilar[1,2,6,*]

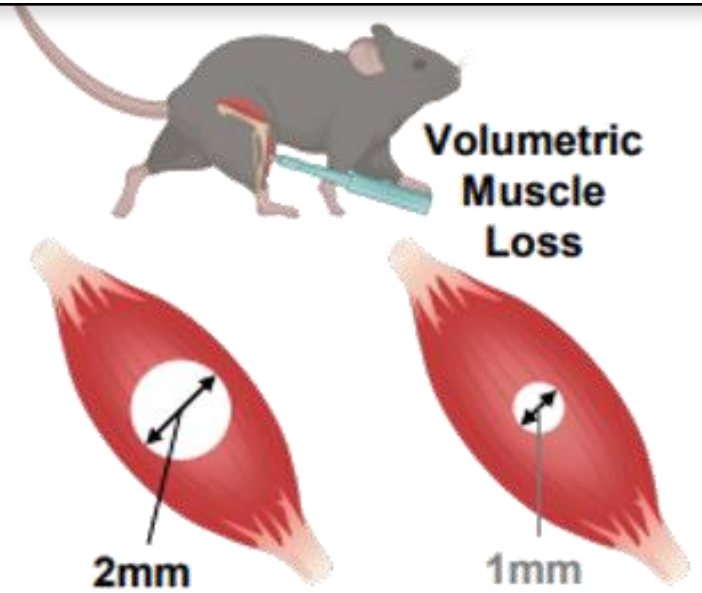
eLife 2023

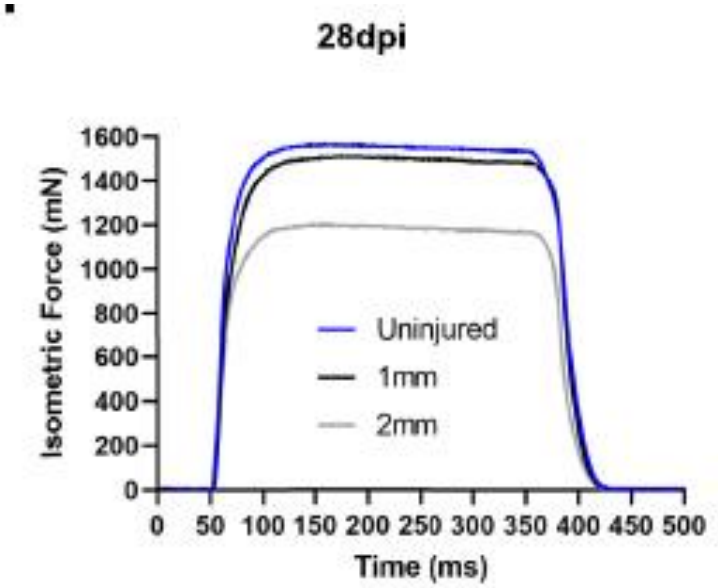
RvD1

- Limited degree of inflammation
- Enhanced regeneration
- Enhanced PMN clearance
- Modulated stem cell response

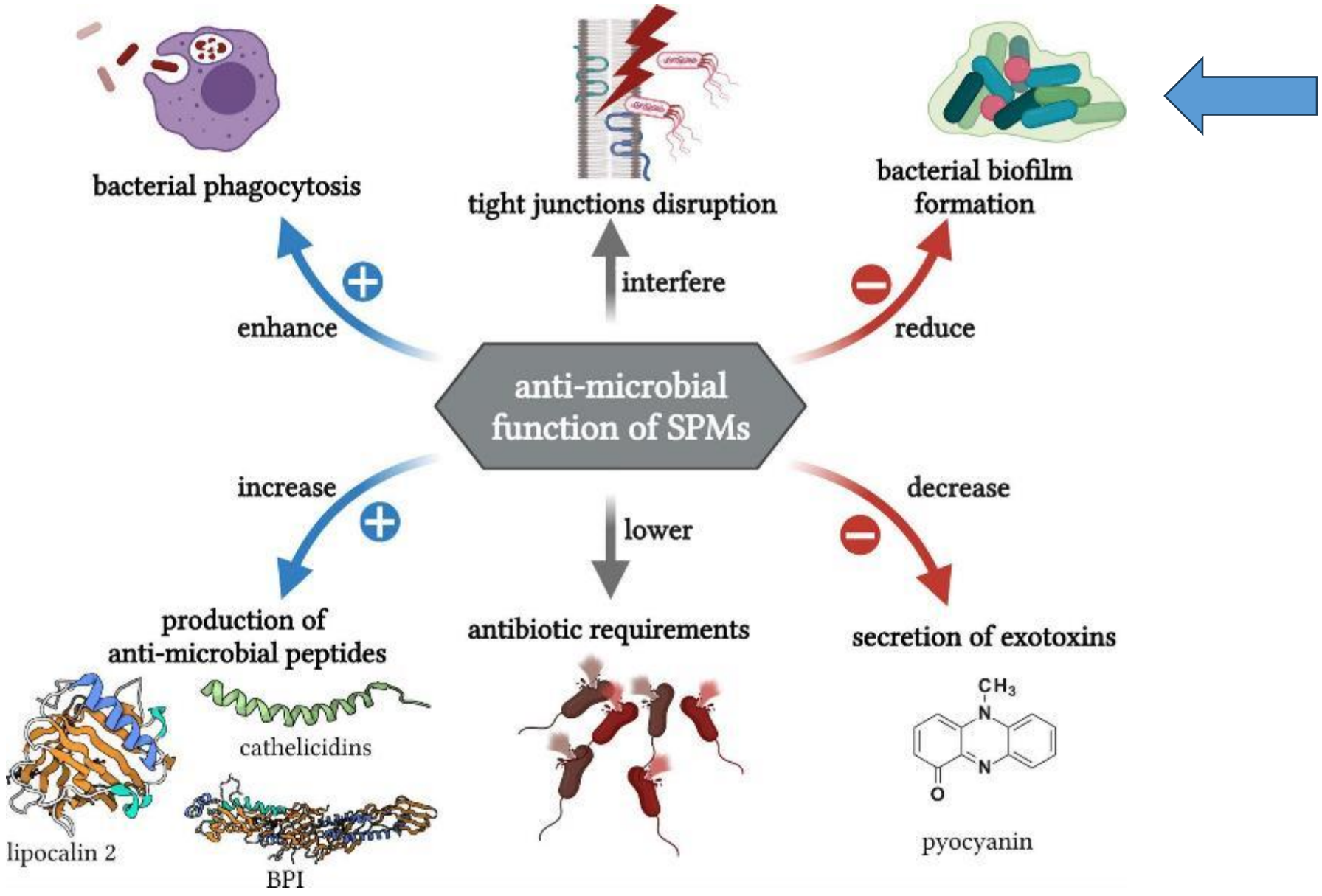
Tx with Maresin 1

- Augments macrophage polarization (conversion from M1 to M2)
- Ameliorates fibrosis
- Improved myogenesis
- Enhanced recovery of muscle strength





Major Antimicrobial Functions of SPMs, Both Direct and Indirect Effects



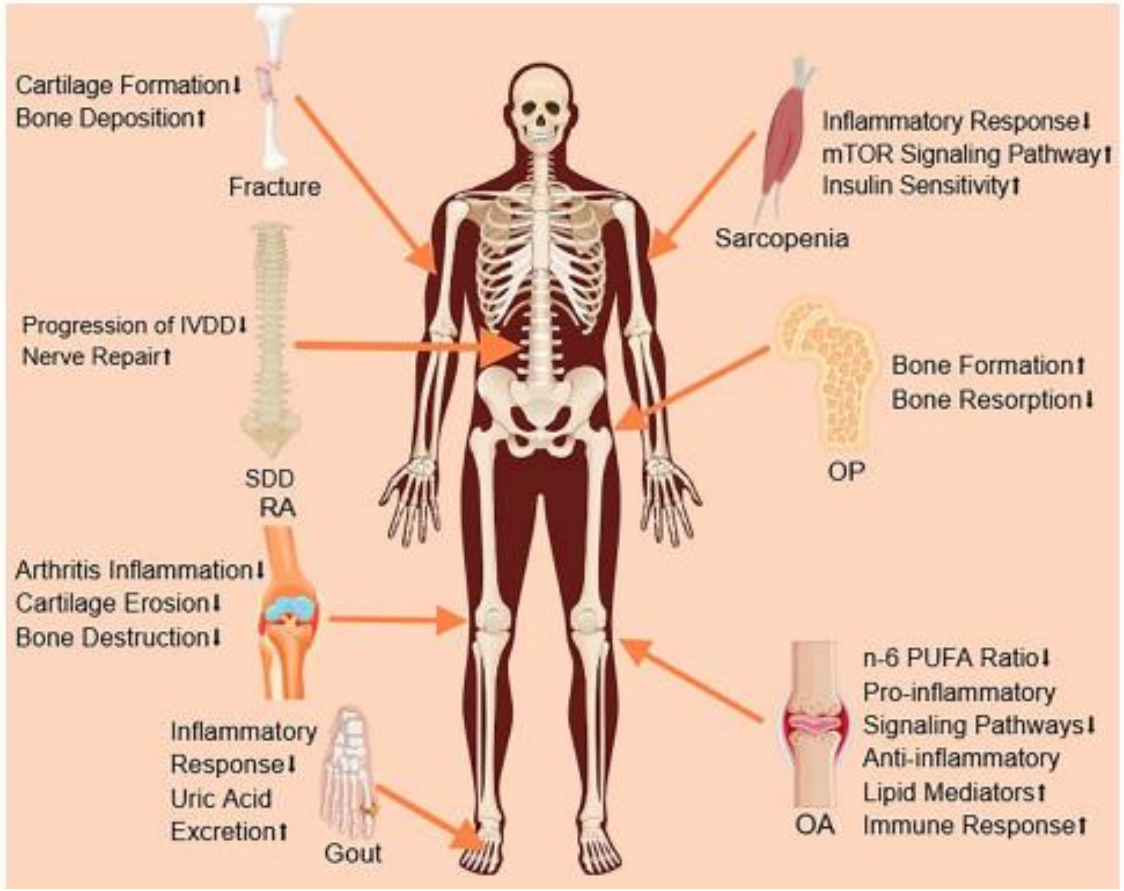
BPI = bactericidal/permeability-increasing protein

Jordan PM, Werz O. The FEBS Journal 2021

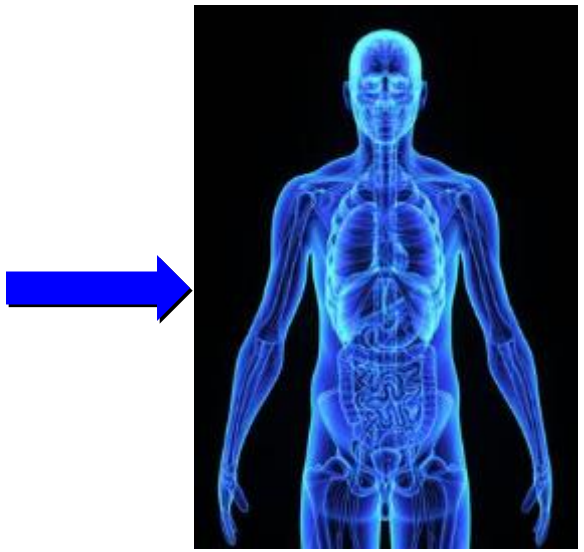
The research progress and potential applications of *n*-3 fatty acids in orthopaedics: a narrative review

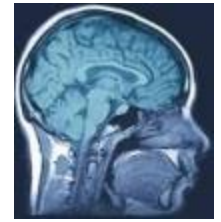
Mao H, Lu G, Zheng L et al

British J Nutrition 2025



Modulating the Microbiome in Ortho Surgery:
Can We Do It ? Does it really matter ?

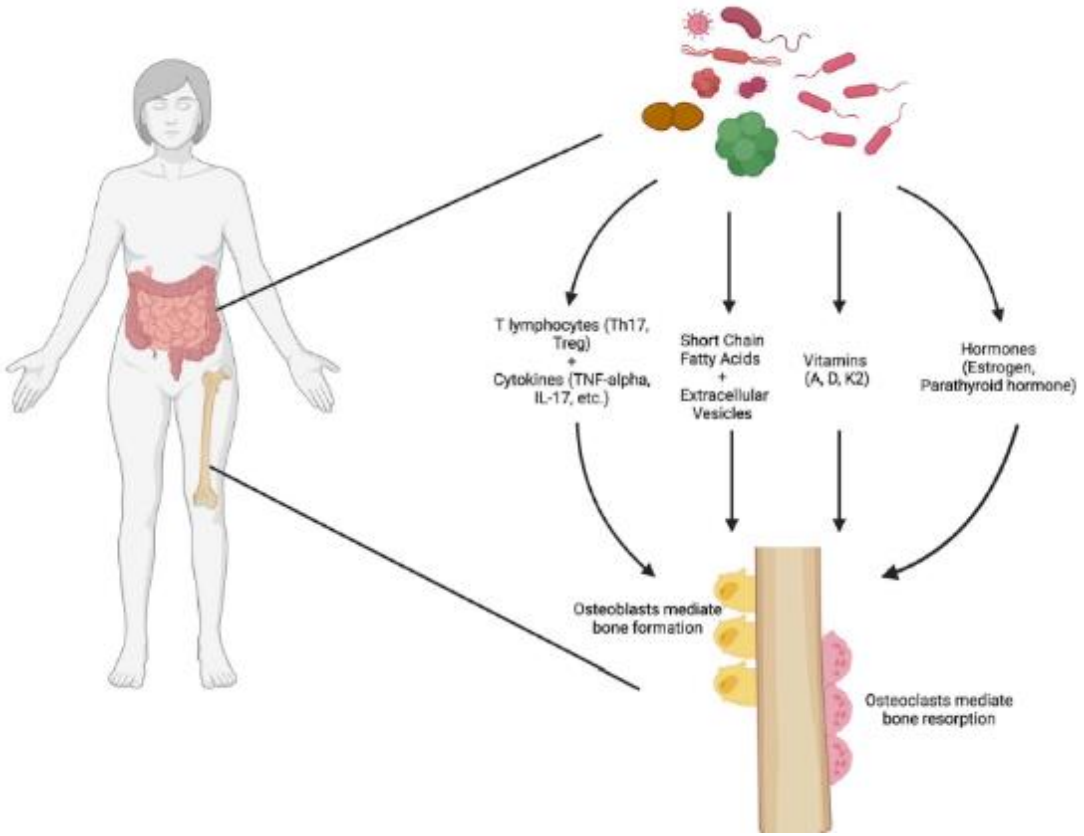


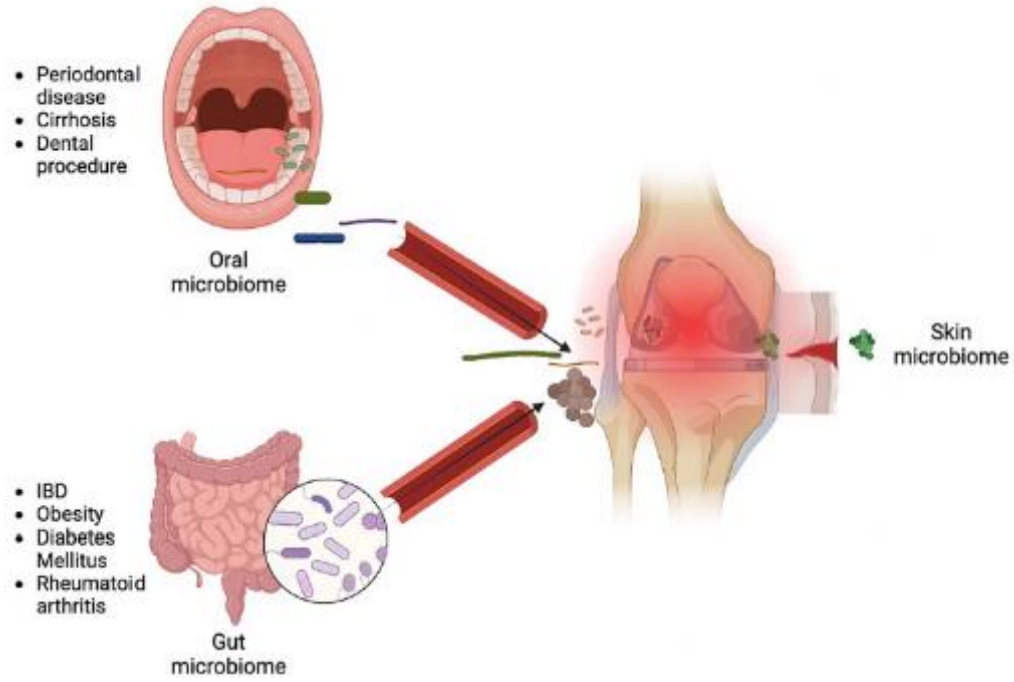


JB&JS OPEN ACCESS
2024

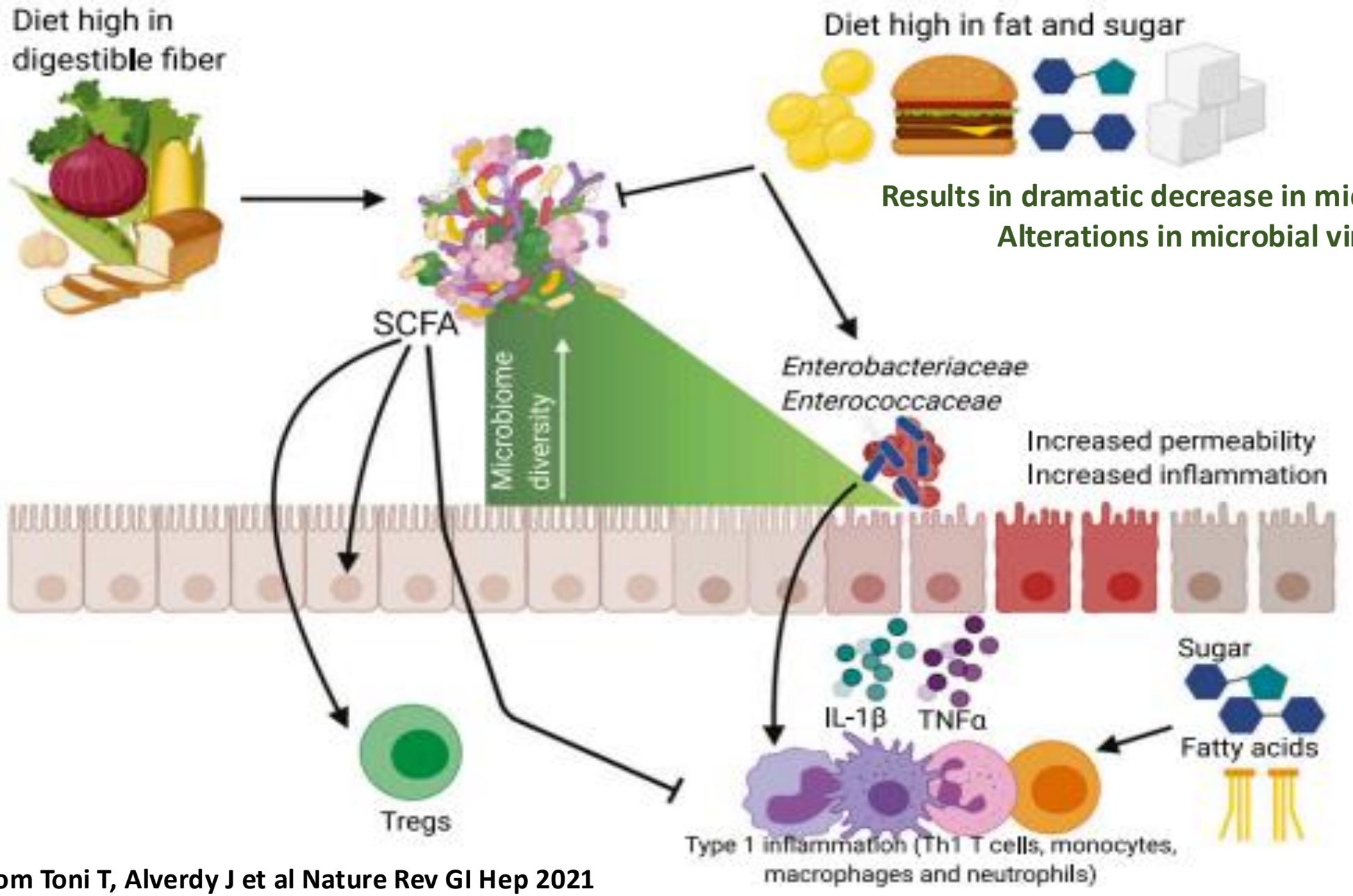
The Microbial Revolution in the World of Joint Replacement Surgery

Arjuna Srikrishnaraj, MSc, Brent A. Lanting, MD, Jeremy P. Burton, PhD, and Matthew G. Teeter, PhD

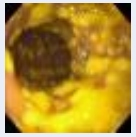
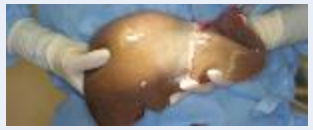




Are post op patients set up for excessive inflammatory response- ??



Modified from Toni T, Alverdy J et al Nature Rev GI Hep 2021

Clinical Condition	Probiotic	References
Antibiotic associated diarrhea 	*L casei, LGG,* *L plantarum* *S Boulardii*	Hempel 2012,Morrow 2012 Barraud 2013, Surawicz 2009, Doron 2008, Hickson2007, Alberda 2018
C. difficile 	*LGG, S.Boulardii* *Numerous*	Na 2011, Katz 2006, Johnson 2012, Shen NT 2017, Johnson 2018, Bommiasamay Am J Surg 2018
Ventilator associated pneumonia 	*L. rhamnosus* GG *L casei, Bifidobacterium bifidum*	Bo 2014 – Cochrane review Morrow 2010, Barraud 2010 Giamaerellos Bourboulis 2009 Knight 2009, Forestier 2008, Shimuzu 2018
Abdominal surgery, Liver transplant 	*L plantarum* 299v *L casei B breve* *L rhamnosus*	Rayes 2002, 2005, Chanmao 2007, Kanazawa 2005, Sugawara 2006, Horvat 2010, Liu 2011, Eguchi 2011, Lytvynl 2016
Sepsis 	*L plantarum* *L casei, L rhamnosus*	Panigranhi 2017, Arumugam 2016, Sun 2017, Argenta 2016
Trauma 	*Bifidobacterium breve, L rhamnosus* *L casei*	Kotzampassi 2006, Spindler-Vesel 2007, Tan 2011, Tariq 2025
Orthopedic Surgery 	*Multiple*	Tariq et al 2025, Zhang X et al 2023, Dahshan D 2022, Sharma DK et al 2024, Hu L et al 2023

Perioperative Probiotics or Synbiotics in Adults Undergoing Elective Abdominal Surgery

A Systematic Review and Meta-analysis of Randomized Controlled Trials

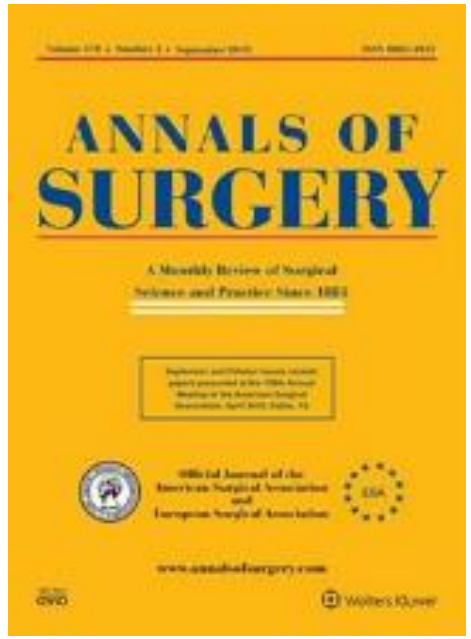
Abeed H. Chowdhury, PhD, FRCS, Alfred Adiamah, MRCS,* Anisa Kushairi, BMedSci, BM BS,* Krishna K. Varadhan, PhD, MRCS,* Zeljko Krznaric, MD, PhD,† Anil D. Kulkarni, MSc, PhD,‡ Keith R. Neal, DM, FRCP,§ and Dileep N. Lobo, DM, FRCS, FACS, FRCPE*¶*

2020

34 RCT n=2753

1354 treated with Synbiotics or Probiotics
1369 control

Synbiotics and Probiotics decrease risk of infections 56% p<0.00001
Synbiotics > than probiotics alone p<0.00001

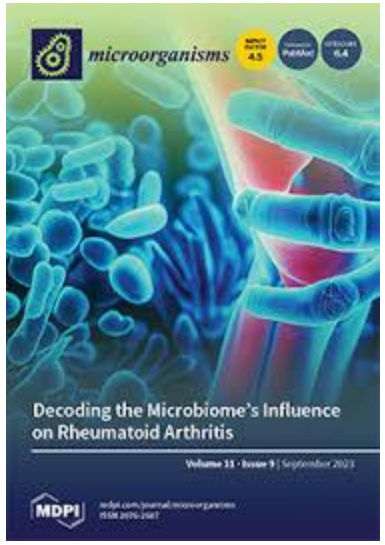


Conclusions:

1) **Synbiotics and Probiotics decrease infections, LOS**
   - **No adverse effects**
2) **No change in mortality**

Probiotics in Orthopedics: From Preclinical Studies to Current Applications and Future Perspective

Antonio Mazzotti [1,2], Laura Langone [1], Alberto Arceri [1,*], Elena Artioli [1], Simone Ottavio Zielli [1], Simone Bonelli [1], Pejman Abdi [1] and Cesare Faldini [1,2]



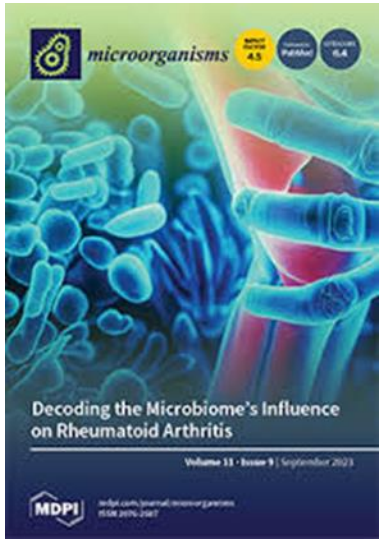
Mazzotti A et al Microoganisms 2023

Summary of studies concerning muscle

Study	Study Population	Probiotic Strain	Duration of the Treatment	Results
Hsu et al. [45]	32 male mice	*Lactobacillus fermentum* DSM 32784 (LF26), *L. helveticus* DSM 32787 (LH43), *L. paracasei* DSM 32785 (LPC12), *L. rhamnosus* DSM 32786 (LRH10), and *Streptococcus thermophilus* DSM 32788 (ST30)	4 weeks	Supplementation alters the gu microbiota composition, improv performance, and combats physical fatigue.
Toohey et al. [46]	23 female athletes (19.6 ± 1.0 years, 67.5 ± 7.4 kg, and 170.6 ± 6.8 cm)	*Bacillus subtilis*	10 weeks	No effect on physical performan but may improve body compositi
Chen et al. [47]	24 mice	*L. plantarum* TWK10 (LP10)	6 weeks	LP10 significantly decreased fin body weight and increased relati muscle weight, strength, and endurance. Moreover, a decrease lactate, ammonia, creatine kinas and glucose serum levels after ac exercise challenge was observe
rokopidis et al. [48] Systematic review and meta-analysis	/	/	/	Probiotic supplementation enhan muscle mass and strength; no effe on total lean mass.
De Pavia et al. [49] Systematic review	/	/	/	Not enough evidence to support t probiotics can improve performa in endurance and aerobic exercis
Chen et al. [50]	18 female senescence-accelerated mice	*Lactobacillus paracasei* PS23 (LPPS23)	12 weeks	Significant attenuation of age-related decrease in muscle m and strength.
Lee et al. [51]	young mice and old mice	*L. plantarum* HY7715	5 weeks	Inhibition of the sarcopenic proc in skeletal muscle.
Bindels et al. [52]	mouse model of leukemia	*L. reuteri* 100–23 and *L. gasseri* 311,476	/	Reduction in the expression of atrophy markers in muscles.
Varian et al. [53]	$Apc^{Min/+}$ mice and *wildtype* littermates for experiments involving cancer	*Lactobacillus reuteri* ATCC-PTA-6475	/	Symbiotic bacteria through Fox and thymic stimulation provid possible alternatives for cachex prevention.

Summary of studies concerning bone

Study	Study Population	Probiotic Strain	Duration of the Treatment	Results
Narva et al. [29] Randomised double-blind crossover study	20 postmenopausal women (mean age 65, range 50–78)	*L. helveticus*-fermented milk and *L. helveticus*-derived peptides	2 study days and 6 days washout between each study day	*L. helveticus*-fermented milk reduced serum PTH and increased serum calcium. *L. helveticus*-derived peptides had no significant acute effect.
Jones et al. [32] Double-blind, placebo-controlled, randomised, parallel-arm multicenter study	127 healthy hypercholesterolemic adults (ages 20–75)	*L. reuteri* capsules	13 weeks	Serum 25-hydroxyvitamin D increased by 25.5%.
Nilsson et al. [33] Double-blind placebo-controlled study	70 women with low bone mineral density	10^{10} colony-forming units of *L. reuteri* 6475	12 months	*L. reuteri* 6475 reduced loss of total bone mineral density compared to placebo.
Jafarnejad et al. [34] Randomised, double-blind, placebo-controlled clinical trial	50 women (ages 50–72) with mild bone loss	Multispecies probiotic capsules (GeriLact)	6 months	Decrease in bone-specific alkaline phosphatase and in collagen type 1 cross-linked C-telopeptide in serum PTH and TNF-alfa.
Takimoto et al. [30]	76 healthy, postmenopausal women (50–69 years)	*Bacillus subtilis* C-3102 (C-3102)	24 weeks	Significant increase in total hip bone mineral density. Significant decrease in bone resorption markers.
Jia et al. [35] Placebo-controlled intervention clinical trial	126 elderly hospitalised patients with primary osteoporosis	Bifidobacterium quadruple viable that comprises four components of bifidobacterium, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus*	24 months	Decrease in bone Gla protein, total propeptide of type I procollagen, and β-crosslaps. Decrease in phosphate, IL-6 and TNF-α serum levels. Increase in IGF-1.
Lambert et al. [36] Parallel-design, placebo-controlled, double-blind, randomised controlled trial	85 postmenopausal women	Heterogeneous culture of probiotic lactic acid bacteria	12 months	Attenuation of bone mineral density loss. Decrease in plasma concentrations of collagen type 1 cross-linked C-telopeptide. No significant effect on other bone turnover biomarkers.

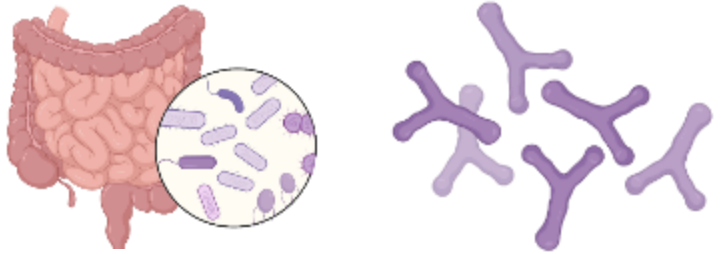


Mazzotti A et al
Microoganisms 2023

Why do current strategies for optimal nutritional therapy neglect the microbiome?

Stephen A. McClave M.D. [a,*], Robert G. Martindale M.D., Ph.D. [b]

- **Current ICU enteral and parenteral nutrition therapy does not specifically address evolutionary interaction and mutualism between host and luminal bacteria**

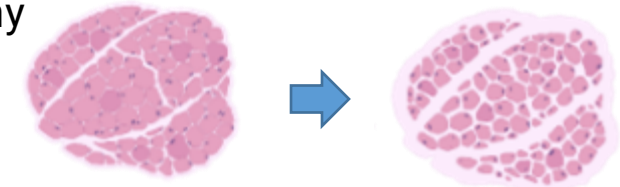


  - **Current dogma has primary concern for:**
    - **Macronutrients (fat, CHO, protein), micronutrients (vitamins and trace minerals)**
    - **Starting to consider gut derived metabolites which can signal cellular responses both locally and systemically (example - butyrate)**
    - **Amount of interactions and crosstalk between microbiome, metabolic end products, host local and systemic immune system, gut epithelial is currently too complex**

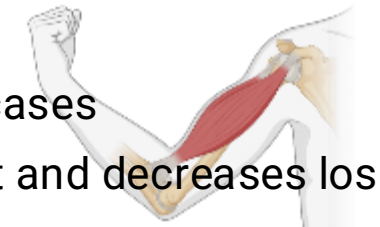
McClave SA, Martindale RG. Nutrition 60:100-105, 2019

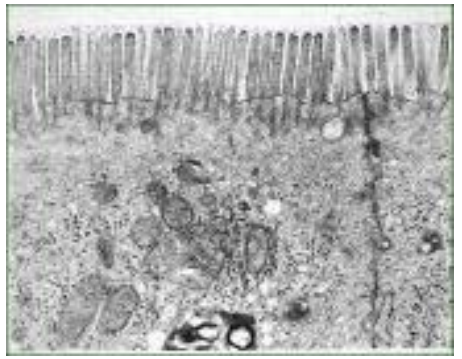
Basic Tenants of Nutritional Therapy in Orthopedic Surgery 2025

- **No data to support routine supplements of vitamins and minerals preop**
- **Nutritional Pre-habilitation now has level 1 data to support in Ortho**
- **Selective immune and metabolic modulation**
  - Decrease length of stay and # of infections
  - FO substrate for SPM production
  - FO to decrease immobilization induced muscle atrophy



- **Maintain lean body mass and function**
  - Resistance exercise ***with*** increase protein intake
    - Growing data for Leucine supplements in elderly
  - Anabolic resistance **can be** overcome in many cases
  - Fish oils preop accelerates muscle recover post and decreases loss in periop period





- **Support healthy microbiome –preventing conversion to pathobiome**
  - Minimize opioids, antibiotics (especially anti-anaerobic antibiotics), PN,
  - Preop dietary prehabilitation is easily applied (low fat / high fiber)
  - EN with soluble and insoluble fibers, possibly multispecies probiotics

Rosenthal M, Martindale R, Moore F Curr Prob Surgery 2015
Adiamah A et al Ann Surg 2019,
McClave, Martindale, Rice, Heyland CCM 2014
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Stoppe C et al Critical Care 2020
Wastyk HC et al Cell 2021

Take home messages

- Consider nutritional intervention at diagnosis / or on admission
  - Prehabilitation clearly works in Ortho surgery
- The highest risk patients are those with sarcopenic obesity and frailty
- Control or modulation of the inflammatory response is a goal
- Anabolic resistance can be overcome

  - Higher protein, timing of delivery, combine with resistance exercise
- Rapid advancement to goal calories should *no longer* be a primary interest
- Immune and metabolic modulation preop / postop *works*

  - Decrease length of stay and decrease infections
- Start considering what "we" do to alter the microbiome
  - Prebiotics, probiotics, synbiotics, postbiotics preventing conversion to pathobiome
  - Attempt to maintain microbiome diversity – fermented foods, fibers
- Be cautious when reading the nutrition literature – reading abstract only is often misleading

‘It is not the strongest or the most intelligent species that survives. It is the most adaptable to change’

Charles Darwin