Skeletal Muscle as a Dynamic Organ that Orchestrates Whole Body Metabolism

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Disclosures

- Danone – Advisory Board
- Smartfish – Research Collaboration
- Abbott Nutrition – Research Collaboration
- Rottapharm – Advisory Board
- Acacia – Research Collaboration
- Santhera – Research Collaboration
Learning Objectives

1. Provide an overview of the relationship between skeletal muscle and metabolism

2. Describe skeletal muscle plasticity in response to environmental and physiological challenges

3. Discuss the clinical implications in muscle wasting conditions
The Muscle and Its Main Functions

**SKELETAL MUSCLE**

- **Main reservoir of proteins**
- **Glutamine synthesis and storage**
- **Regulator of glucose levels**

**METABOLIC FUNCTIONS**

- **Physical movement**
- **Strength**
- **Maintenance of posture and balance**

**EUGMS, 2017**
Average Muscle Mass

38-54% men

28-39% women

40%
Glutamine is Mainly Synthesized and Stored in Skeletal Muscle

- Precursor of neurotransmitter synthesis
- Mainly synthesized and stored in skeletal muscle
- Precursor:
  - Nucleotide and nucleic acid synthesis
  - Glutathione production

- Cell Proliferation
- Antioxidant defense system

- Oxidative fuel
- Substrate for ureogenesis
- Substrate for gluconeogenesis
- Acid-base balance

Skeletal Muscle is a Regulator of Metabolic Homeostasis

Skeletal Muscle Orchestrates Metabolic Events

Complications of Lean Body Mass (Muscle) Loss

-10%: Decreased immunity of infection

-30%: Increased vascularity, increased infection, pressure ulcers, pneumonia, inability to heal

-40%: Increased risk of death, usually from pneumonia

70% of cancer patients suffer from significant muscle loss

1/5 cancer patients die from muscle loss and malnutrition rather than the tumor
Effects of Ageing and Illness on Muscle Mass

- Aging
- Illness
- Malnutrition Risk
  - Anabolic Oxidative resistance stress
  - Reduced physical activity
  - Inflammatory signaling
  - Metabolic disruption
- Decreased protein synthesis
  - Impaired myogenesis
  - Increased protein degradation
- Muscle mass & metabolic atrophy
  - Low force generation
  - Impaired contraction ability
SKELETAL MUSCLE WASTING

INCREASED PROTEOLYSIS

DECREASED PROTEIN SYNTHESIS

INCREASED BCAA OXIDATION

DECREASED AA UPTAKE

DECREASED MUSCLE REGENERATION

INCREASED APOPTOSIS

MITOCHONDRIAL DYSFUNCTION/ SR STRESS
Skeletal Muscle Wasting Crosstalk
**GUT (malabsorption)**
- Gut-barrier dysfunction
- Altered ghrelin production
- Release of inflammatory mediators

**WHITE ADIPOSE TISSUE (wasting)**
- Increased lipolysis
- Release of fatty acids
- Release of inflammatory mediators?

**HEART (cardiac dysfunction)**
- Atrophy
- Decreased innervation
- Increased energy consumption
- Release of inflammatory mediators?

**BRAIN (anorexia)**
- Altered pattern of hypothalamic mediators
- Loss of appetite
- Hyposmia
- Hypogeusia

**LIVER (acute-phase response)**
- Release of acute-phase proteins
- Hypoalbuminaemia
- Release of inflammatory mediators?

**BROWN ADIPOSE TISSUE (thermogenesis)**
- Energetic inefficiency

**SKELETAL MUSCLE (wasting)**
- Decreased innervation
- Increased energy consumption
- Release of inflammatory mediators?

**BONE (resorption)**
- Osteoclast activation

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Skeletal Muscle is Not Just Associated with Contraction

Skeletal muscle as a thermogenic organ

Types of thermogenesis

Shivering

Non-shivering
Sarcolipin Promotes Oxidative Metabolism under Conditions of Increased Energy Demand. During muscle contraction, membrane depolarization leads to activation of DHPR/Ryr1 complex leading to release of Ca$^{2+}$ from the SR.
Skeletal Muscle as an Endocrine Tissue
Functions of Myokines

endothelial cell proliferation

hormone-like effects

capillary

basal lamina

extracellular matrix disassembly reorganization

hypertrophy metabolic effects

satellite cell proliferation, migration

MYOKINES

capillary

myofiber
How Do We Address the Underlying Metabolic Dysfunction Leading To Muscle Loss?

- Inflammation
- Insulin resistance
- Low anabolic hormones
- Low blood flow

Muscle Protein Breakdown

Muscle Protein Synthesis

Net Balance

Drugs?

↑ Muscle Loss

↓ Muscle Gain

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TOXICITY

TOXICITY

TOXICITY

TOXICITY

TOXICITY

TOXICITY
Improved management of cancer cachexia certainly requires a multimodal approach by a multi-disciplinary team and is best commenced earlier rather than later.
Physical activity, especially resistance training stimulates protein synthesis in muscle

Exercise

Nutrition

High-protein diets including EAAs and BCAAs contribute to muscle accretion

The leucine metabolite HMB is a potent stimulator of protein synthesis in muscle
HMB: Ergogenic Nutritional Supplement

Leucine metabolite

Grapefruit, alfalfa, catfish
β-Hydroxy-β-Methylbutyrate (HMB)

- HMB is a natural metabolite of the amino acid leucine\(^1\)
  - Produced in low levels in the body

- Science behind HMB
  - Originated in the ‘Sports Nutrition’ world
  - Studied in relation to disease states and older adults for over 15 years\(^2\)
  - Ca-HMB is Generally Recognized As Safe (GRAS) up to 6 g/day

Most referenced dose 3 g/d (Ca-HMB), no safety issues \(^{1,2,3}\)
Metabolism of HMB in the Body

**LEUCINE**

- BCAA transferase
- BC-Keto acid Dehydrogenase

**α-Ketoisocaproate (KIC)**

- ~95%

**Isovaleryl CoA**

**β-methyl crotonyl-CoA**

**β-methyl glutaryl-CoA**

**β-hydroxy-β-methyl glutaryl-CoA (HMG-CoA)**

- HMG-CoA Lyase

**β-Hydroxy-β-methyl butyrate (HMB)**

- Circulates to muscle

- 0.5-5% KIC dioxygenase
- 10-40% in Urine

**HMB-CoA**

- HMG-CoA

**Mevalonate**

**Cholesterol**

**Acetoacetate + Acetyl CoA**

**HMG-CoA**

Mechanisms
β-hydroxy-β-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions

- Inhibits ubiquitin-proteasome system (↓ proteolysis)
- Stimulates mTOR pathway (↑ protein synthesis)
- Inhibits autophagy-caspase system (↓ apoptosis of myonuclei)
- ↑ GH and IGF-1 (↑ protein synthesis and ↓ proteolysis)
- ↑ cholesterol synthesis (↑ tissue repair)
- ↑ calcium release from SR (improves excitation-contraction coupling)
- ↑ proliferation of satellite cells (↑ tissues repair)
- ↑ mitochondrial biogenesis (↑ aerobic performance)

Holecek, M. J. Cachexia Sarc. Muscle., 2017
Developing Muscle Wasting (Atrophy)-Specific Nutritional Approaches

Objectives

- Increase body weight
- Stimulate food intake
- Decrease inflammation
- Decrease energy expenditure
- Enhance absorption/Gastric emptying
- Preserve LBM (anabolic + anticatabolic)
- Enhance QoL
- Control disease
- Increase survival
## Take Home Messages

| Skeletal Muscle as a metabolic organ | • Skeletal Muscle:  
| | • Orchestrates metabolic events  
| | • Regulates metabolic homeostasis  
| | • Serves as an important thermogenic, metabolic, and endocrine organ |
| Skeletal Muscle wasting in disease | • Skeletal Muscle wasting is associated with morbidity and mortality |
| Nutrition and Skeletal Muscle wasting | • Conventional nutrition is unable to reverse muscle wasting  
| | • Use of drugs is associated with toxicity |
| Nutraceuticals: HMB | • Combination of nutritional approaches (including nutraceuticals) with exercise has important potential in treatment of muscle wasting  
| | • HMB: ↑ body weight, stimulates food intake, ↓ inflammation, and may serve to preserve LBM |