OPTIMISING NUTRITION FOR AGEING MUSCLES: NUTRIENTS BEYOND PROTEIN

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This presentation aims to...

1. Emphasize the importance of skeletal muscle size and quality for healthy ageing.

2. Briefly review best protein nutrition practice for ageing muscles.

3. Evaluate the biological rationale and existing scientific evidence base for emerging nutrients and/or neutraceuticals related to promoting the health of ageing muscles.

4. Highlight gaps in research knowledge for the nutrition industry and academia to exploit with regards to the active ageing market.
The importance of **muscle** size and quality extends beyond performance nutrition

**PERFORMANCE NUTRITION**
- Strength sports
- Power: mass
- Aesthetics

**ACTIVE NUTRITION**
- Healthy ageing
- Child growth
- Healthy weight loss
- ↓ Diabetes risk
- ↓ Obesity risk

**HEALTH AND WELLNESS**
- Better choices, more often

Ageing is associated with a gradual loss of skeletal muscle mass that is exacerbated by periods of muscle disuse.

“Threshold of disability”
The market space of active ageing extends beyond 65 years plus.
What is the definition of sarcopenia?

“The progressive decline in skeletal muscle mass (myopenia) and strength (dynapenia) that predisposes reduced muscle function with advancing age”
The cause of sarcopenia is clearly multifactorial, interconnected and complex.

- **Exercise**
  - Anabolic Resistance
  - Inactivity
  - Motor Units
  - Oxidative Stress
  - Satellite Cells
- **Nutrition**
  - Insulin Resistance/Blood Flow
  - Injury/Illness
  - DNA Damage/Apoptosis
  - Hormonal Changes
  - Low grade inflammation

AGE 25 vs. AGE 65

Morley 2012 Fam Practice
What is muscle protein synthesis and why should the nutrition industry care in terms of healthy ageing?
The response of muscle protein synthesis to amino acid feeding is impaired in older adults.
Low-grade inflammation impairs the stimulation of muscle protein synthesis in response to food intake

- 2 groups of rats: low grade inflamed (LGI) group and a control non-inflamed (NI) group
- Muscle (gastrocnemius) protein synthesis
- Fasted and fed state

Balage et al. 2010 J Nutr Biochemistry
The magnitude of the “muscle protein synthetic” response to ingested protein is regulated on several levels of physiology.
The ‘optimum’ protein **dose** for maximal stimulation of muscle protein synthesis increases with advancing age.

**Witard et al 2014 Am J Clin Nutr**

**Yang et al 2012 Br J Nutr**
The potential **drawback** associated with recommending increased daily protein intakes in older adults

- Older (64 years old) women
- 9 wk dietary control
- En% protein - 15% vs 30%

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**Graphs:**

- **Hunger (VAS: 1-100):**
  - 15% vs 30%

- **Fullness (VAS: 1-100):**
  - 15% vs 30%

Leidy *et al.* 2007 *Obesity*
How can industry and academia collaborate to overcome age-related anabolic resistance?

Optimising the response of MPS

- Maximise anabolic potency
  - Daily protein intake
  - Meal-by-meal protein intake

- Enhance anabolic sensitivity
  - Prior exercise
  - Coingesting other nutrients

Nutrients and compounds:
- Leucine
- Creatine
- Anti-inflammatory nutrients
- Vitamin D
- Antioxidants
- N-3 PUFA
- Curcumin
- Resveratrol
- Vitamins C and E
- Arginine
- Citrulline
- Nitrates
- Neutera-ceuticals
- Alcohol
- Ca⁺ Free acid
- β-HMB
- Sodium nitrate
- Ursolic acid
- Phosphatidic acid
Fish oil supplementation potentiates the response of muscle protein synthesis to simulated feeding in older adults

- Healthy active young men (n=5) and women (n=4)
- 8 weeks of fish oil derived n-3 PUFA supplementation
  - 4 g/day fish oil capsules
  - 1.86 g/day EPA and 1.50 g/day DHA
- Basal and stimulated measurements of MPS

Mixed muscle protein synthesis (%/h)

- Basal and Fed measurements of MPS before and after n-3 PUFA supplementation

Smith et al. 2011 Clinical Science,
EPA is the “anabolic” component of fish oils

- C2C12 myotubes
- Incubated with ethanol (control), EPA or DHA
- Stimulated by leucine
- Protein synthesis and protein breakdown

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Resveratrol may protect against the age-related loss of muscle loss via anti-inflammatory properties

- C2C12 myotubes (a mouse cell line)
- Treated with TNF-α
- Incubated with or without resveratrol
- Direct and indirect markers of muscle atrophy

Wang et al. 2014 Int Immunopharmacology
Vitamin D is taken up and stored in skeletal muscle cells

Tracer uptake of 25(OH)D

Abboud et al. 2013 Endocrinology
Vitamin D has been shown to enhance the MPS response to an anabolic stimulus

- C2C12 myotubes
- Control (unstimulated cells)
- Ins+Leu (stimulated with leucine and insulin only)
- Ins+Leu+VitD (cultured in 1,25(OH)2D3 for 72 h)
Curcumin may protect against muscle loss in older adults by reducing muscle inflammation and oxidative stress

- Old mice injected with streptozotocin to induce T1D
- 2 weeks of diet with or without curcumin (1500 mg kg\(^{-1}\) day\(^{-1}\))
- Measurements of skeletal muscle weight and myocyte cross-sectional area

Ono et al. 2015 Exp Phys
Biological rationale behind the potential for nitrates to enhance the MPS response

INGESTED PROTEIN SOURCE

a) Protein digestibility
b) Amino acid absorption kinetics

1. Blood amino acid availability

   a) Blood flow
   b) Capillary recruitment
   c) Microvascular perfusion

2. Amino acid delivery to skeletal muscle

   Amino acid transporters

3. Amino acid uptake by skeletal muscle

   Leucine

4. Anabolic cell signaling

   (MYOFIBRILLAR) MUSCLE PROTEIN SYNTHESIS

   LAT1
   MAP4K
   mTORC1
   p70S6K1
   4E-BP1
   4. Anabolic cell signaling
Rationale behind the potential for nitrates (arginine, citrulline and sodium nitrate) to enhance the MPS response

Dietary nitrate supplementation

↑ Nitric oxide availability

↑ insulin delivery

↑ muscle perfusion and capillary action

(MYOFIBRILLAR) MUSCLE PROTEIN SYNTHESIS
Sodium nitrate and protein coingestion: findings from pharmacological and physiologically relevant studies

Dillon et al. 2011 Am J Phys,

Kouw et al. 2016 Am J Phys,
Take home messages:
Optimising nutrition for older muscles

- **Maximise anabolic potency**
  - Daily protein intake
  - Meal-by-meal protein intake

- **Enhance anabolic sensitivity**
  - Prior exercise
  - Coingesting other nutrients

- Optimising the response of MPS
  - Leucine
  - Creatine
  - Anti-inflamm. nutrients
  - Vitamin D
  - Antioxidants
  - Nitrates
  - Neutra-ceuticals
  - Alcohol
  - β-HMB
  - N-3 PUFA
  - Free acid
  - Ca+
  - Resveratrol
  - Curcumin
  - Arginine
  - Citrulline
  - Vitamins C and E
  - Sodium nitrate
  - Ursolic acid
  - Phosphatidic acid
  - N-Acetylcysteine
What opportunities exist for industry-academic partnerships in context of healthy musculoskeletal ageing?

1. Can fish oil supplementation enhance the response of MPS to protein ingestion in active older adults? Protection against muscle disuse?

2. Can vitamin D supplementation enhance the response of MPS to protein ingestion in active older adults?

3. Can the anti-inflammatory and antioxidant nutrients such as resveratrol and curcumin protect ageing muscles against sarcopenia?

4. Is there a role for other neutraceutical compounds such as phosphatidic acid and ursolic acid in reducing the age-related loss of muscle mass?
Acknowledgements
Thanks for listening

.......... any questions?

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Additional slides
What criteria should be used to diagnose sarcopenia?

1. Measure gait speed
   - Older adult (> 65 years)
   - > 0.8 m/s
   - ≤ 0.8 m/s

2. Measure grip strength
   - Normal
     - ♂ ≥ 30 kg
     - ♀ ≥ 20 kg
   - Low
     - ♂ ≤ 30 kg
     - ♀ ≤ 20 kg
   - Sarcopenia

3. Measure muscle mass
   - Low
     - ♂ ≤ 7.25 kg/m²
     - ♀ ≤ 5.67 kg/m²
   - Normal
     - ♂ ≥ 7.25 kg/m²
     - ♀ ≥ 5.67 kg/m²
   - Sarcopenia
   - No sarcopenia

Report of the European working group on sarcopenia in older people
What are prevalence estimates of sarcopenia?

1. On average, 5-13% of older adults aged 60-70 years are affected by sarcopenia.

2. On average, 11-50% of older adults aged 80+. Briefly review best protein nutrition practice for ageing muscles.

3. What about 40 and 50 year olds?
What is mTOR and why should we care in terms of healthy ageing?

↓ energy status

Insulin

Hypoxia

Exercise

EAA (Leucine)

- mTORC1
  - TSC1
  - TSC2
  - BNIP-3
  - MAP4K3
  - hVps34

- REDD1/2

- Akt

- AMPK

- p70S6K1

- 4E-BP1

- MYOFIBRILLAR PROTEIN SYNTHESIS

Drummond et al 2009 J Appl Phys
What is the biological rationale for leucine fortification?

**Diagram**

- **Insulin**
  - **AMPK**
  - **Akt**
  - **mTORC1**
    - **p70S6K1**
    - **4E-BP1**

- **Hypoxia**
  - **REDD1/2**
  - **BNIP-3**
  - **MAP4K3**
  - **hVps34**

- **Exercise**
  - **TSC1**
  - **TSC2**

- **↓ energy status**

**Legends**

- EAA (Leucine)
- Drummond et al. 2009 J Appl Phys
**Fortifying a suboptimal protein dose with leucine “rescues” a submaximal response of muscle protein synthesis**

- Study cohort of older women (~65 years old)
- Acute bout of single-leg resistance exercise
- Meal-like whey protein dose vs. leucine enriched suboptimal EAA dose

![Graph showing muscle protein synthesis (%/h) for WP and L-EAA in Fed and Fasted conditions.](image)
Leucine and HMB ingestion stimulates muscle protein synthesis at rest in young men

- Active young (~26 years) men
- Leucine (3.42 g L-leucine + ~400 mL water)
- HMB (3.42 g free-acid form β-hydroxyl-β-methylbutyrate)
- HMB (3 g calcium form β-hydroxyl-β-methylbutyrate)

Alcohol consumption impairs the MPS response to protein ingestion during exercise recovery

- Physically-active young adults
- Rex + EE + HIIT
- 25 g whey protein or 25 g whey protein + 1.5 g/kg BM alcohol
- Resting and post-exercise measurements of MPS

Parr et al. 2014 PlosOne
Mixed findings from studies examining the ergogenic role of phosphatidic acid on muscle growth.

Joy et al. 2014 Nutr and Metab

The incorporation of EPA/DHA into the muscle phospholipid membrane upregulates **anabolic cell signaling**

McGlory et al. 2014 Prostaglandins Leukot. Essent. Fatty Acids,

Smith et al. 2011 Clinical Science
Fish oil supplementation enhances exercise training induced strength gains in older women

- Healthy older (~64 years old) women
- 90 d strength training with or without fish oil supplementation
  - 2 g/day fish oil capsules
- Pre and post measurements of muscle mass, strength and power

Knee flexor peak torque (Nm)

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Rodacki et al. 2012 Am J Clin
Muscle loss with ageing is underpinned by a **negative net muscle protein balance**.

Area of B > Area of A = Decrease in muscle mass

Redrawn from Phillips et al. 2005 JACN