Treatment of sarcopenia: latest developments

Dr Miles D Witham
Clinical Reader in Ageing and Health
University of Dundee
What’s the point in treating sarcopenia?

- Sarcopenia is associated with a range of adverse outcomes
- Key contributor to frailty phenotype

- Improving physical function and reducing disability are priorities for older people
- The corollary of this is that the focus in treating sarcopenia has to be on improving physical function and reducing adverse outcomes

Roberts H et al. Age Ageing 1994; 23: 154-7
Some caveats

- Very few trials enrolling people with sarcopenia
- So much evidence is not directly translatable
- Previous trials have enrolled:
  - Healthy older people
  - Older people with functional impairment
  - Older people with low walk distances
  - Older people who fall
- If it ain’t broke, you can’t fix it…
What works?

- **Exercise**
  - *Resistance training* can improve muscle mass and muscle strength in sarcopenia
  - Evidence from multiple RCTs
  - Less known about how we make this happen in clinical practice

- **Vitamin D (a bit, probably)**
  - Grip strength: SMD 0.01 (-0.06 to 0.07; p=0.87)
  - Lower limb strength: SMD 0.19 (0.05 to 0.34; p=0.01)
  - Muscle mass: SMD 0.06 (-0.19 to 0.31; p=0.66)

Cruz Jentoft et al. Age Ageing 2014; 43: 748-59
Beaudart et al. JCEM 2014; 99: 4336-45
What is unlikely to work?

- Antioxidant vitamins – difficult to ingest the amount needed to produce a biological effect
- Growth hormone – increases muscle mass in deficiency states, but not muscle strength
- Testosterone – improves muscle mass and strength in healthy older men. Side effects a problem
- Aerobic exercise – improves cardiorespiratory fitness but little effect on maximal muscle strength or muscle mass. Still has a role in improving function though.
What might work?

- ACE inhibitors
- Protein supplementation
- Leucine
- Creatine
- Myostatin inhibitors
- Inhibitors of ROS generation
- Testosterone
ACE inhibitors

- Angiotensin II has effects on muscle
  - affect phosphorylation of myosin heavy chains
  - Enhance glucose uptake (bradykinin)
  - Complex effects on uncoupling protein activity in mitochondria, with reduction in oxidative stress
  - IGF-1 production is under partial control of Angiotensin II (downregulates)
  - ACE inhibitors reduce TNF levels in heart failure
- Observational data suggest an association between ACEi use and preserved walk speed
- No association with grip strength though
Effect of ACE inhibitors on muscle function in older people

Sumukadas et al. CMAJ 2007; 177: 867-74
Protein supplementation

- Variable results!
- May not do much on its own
- May enhance the effect of resistance training – results inconclusive
- Problem of dose – anabolic resistance in older muscle so may need more protein than can reasonably be taken
- Homeostatic compensation – reduction in protein intake in normal meals
Leucine

- Some evidence that leucine might improve muscle strength in older people
- Certainly improves amino acid uptake and incorporation by muscle
- May not add much to resistance training
- More effective than other amino acids – appears to facilitate uptake and overcome anabolic resistance in older muscle
Creatine

- Data mostly from healthy older adults
- Supplementation can augment effect of resistance training
- Fat free mass +1.3 Kg (95% CI 0.8 to 1.9; p<0.001)
- Improved chest press (+1.7Kg); leg press (+3.3Kg)
- No effect on knee extension or biceps curl
- Increased chair stands in 30s (1.9 stands; 95% CI, 0.2 to 3.7; p=0.03)

Devries et al. MSSE 2014; 46: 1194-1203
- Older women with Rockwood CFS 4 or worse
- 2x2 study: Creatine vs placebo; RT vs no RT
- 1 rep max leg press as main outcome; TUAG as well

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Leg press | Appendicular lean mass | TUAG

Multicomponent nutritional interventions

- PROVIDE: Whey+leucine+vitamin D for 13 wks vs placebo; no training
  - SPPB 4 to 9; low %skeletal muscle mass. NOT sarcopenic
  - No improvement in SPPB or grip strength
  - 1.0s improvement in chair-stand test; 0.2Kg increase in muscle mass
- Rondanelli: Whey+AA's+Vitamin D for 12 wks vs placebo; resistance training for all
  - Sarcopenia
  - 1.7Kg increase in muscle mass

Bauer et al. JAMDA 2015; 16: 740-7
Myostatin inhibitors

- Myostatin acts as a brake on muscle differentiation, hypertrophy and protein synthesis
- Range of different approaches to inhibiting the pathway: direct inhibitors, activin II receptor blockers
- Some evidence that myostatin inhibition leads to increases in muscle mass – increases in strength may take longer
- Trial in older, weak patients with history of falling:
  - Increase in muscle mass at 24 wks (+0.43Kg; p<0.001)
  - Improved stair climb time, chair stands and fast gait speed
  - No improvement in SPPB, 6 min walk, grip strength

Inhibitors of ROS generation

- Excessive ROS generation may impair mitochondrial function and hence contribute to sarcopenia
- However some ROS needed for training response
- Also need ROS generation for immune-mediated killing
- Allopurinol is a powerful inhibitor of ROS generation by xanthine oxidase
- Improves vascular function via this mechanism
- Associated with improved outcomes in older patients undergoing rehabilitation
ALFIE trial

- Single centre RCT; 600mg allopurinol vs placebo
- 124 participants aged 65 and over; six min walk distance of <400m
- $^{31}$PCr recovery rate by MRI as primary outcome
- Measures of muscle mass and function included in trial
Testosterone

- Improves muscle mass and strength in healthy older men
- Some evidence of effect in women and in frailer older people
- Concern about side effects (esp CV disease)
- Recent Testosterone trials (TTT): borderline improvement in six minute walk with treatment
- Not been trialled in people with sarcopenia though.
So what might a future treatment algorithm look like?

- Sarcopenia
  - Willing / able to do resistance training
    - Combined protein/ AA / vit D interventions
      - Creatine
      - Testosterone?
      - ACEi?
      - Leucine?
      - Myostatin inhibitors?
  - Unwilling / unable to do resistance training
    - (Vitamin D)
Key unresolved issues

- How do we identify most likely candidates?
- What surrogate markers for response might we use?
- How do we find people with sarcopenia to offer trials to?
- What outcomes really matter?
  - Muscle mass?
  - Measures of physical performance?
  - ADLs?
  - Falls?
  - Institutionalisation?
  - Need for care?
- What does the muscle mass component really add?
- How do we make this all happen in practice?
The LACE trial

- Leucine and ACEi in sarcopenia
- 2 x 2 factorial multicentre RCT (15 UK centres)
- 440 patients with sarcopenia aged 70 and over
- 1 year of treatment; placebo controlled
- Perindopril 4mg od vs placebo; leucine 2.5g tds vs placebo
- Primary outcome: change in SPPB
- Other outcomes including muscle mass, falls, QoL, health economics

www.lacetrial.org.uk
Currently recruiting

Looking for 5 additional centres

Minimum of 10 patients randomised per centre; would like 30 ideally

We will provide the kit (including BIA for muscle mass screening)

Need access to DEXA, a -80C freezer plus a trials pharmacist

Join us!
Setting priorities for the SIG

- A scientific meeting
- A catalogue of ongoing research projects
- What should the SIG be doing in research:
  - Recruiting to sarcopenia trials?
  - Setting up a UK-wide frailty cohort / trial platform?
  - Setting up a writing group for grant applications?
  - Supporting health services research on frailty management – and if so, how?
- Mapping how frailty is diagnosed / screened for across the UK?
- Other methods of knowledge diffusion?