Sarcopenia - current limits of its reversibility

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Prevalance of Sarcopenia


13 – 24% > 60 years

> 50% ≥ 80 years
Sarcopenia


40 - 70 years muscle ↓ by 8 % per decade

>70 accelerates to 15 % ↓ per decade

until 70 years leg strength ↓ by 10–15 % per decade

> 70 years ↓ by 25–40 % per decade
Aging, muscle mass and strength


- ↓ of muscle mass and strength by 1% to 2% ≤ 50 years per year
- ↓ 1.5 to 5% > 50 years per year
Sarcopenia – interdisciplinary challenge

Therefore we need a simple interdisciplinary practical classification (SPC)?
Proposal of functional classification of sarcopenia

1. Fundamental Sarcopenic Dysfunctions (FSD)

2. Selective Sarcopenic Muscles Dysfunctions (SSMD)
FSD - GHB

Gait

Hand

Balance

- core stability – ability to control the movements and position of trunk
- foot stability
FSD - Balance
SSMD

- Disuse
- Injury
- Mixe
SSMD - osteoarthritis in the knee

(Laurence and Felson et al., Arthritis Rheum., 2008)

over the age of 45 - 27% of population

by the age 65 - 80% of population
Sarcopenia is not as important as its modulators

Activators  ↔  Inhibitors
Sarcopenia is not as important as its modulators

Activators

- stimulation
- progression
- acceleration of progression
Sarcopenia is not as important as its modulators

Inhibitors

- stimulation of regression
- ↓ progression
- ↓ acceleration of progression
The fate of sarcopenia - 5 key activators

- Health status (multifactorial)
- Medications (multifactorial)
- Physical activity
- Nutrition
- Genetics and epigenetics (multifactorial)
Helth status - Metabolic syndrom

[Grundy SM. Arterioscler Thromb Vasc Biol 2008]

- > 50 years of age, affects more than 40% of the population in the United States [Ford et al. Diabetes Care 2004]

- > 50 years nearly 30% in Europe [Cameron et al. Endocrinol Metab Clin North Am 2006]
Health status

Obesity

↓ the muscle satellite cell
DNA content and cell turnover

↓ muscle fibre loss

Health status - Diabetes

≥ 30 years

- 13.7% - male men
- 11.7% - female

- 32% of all diabetes cases in 2003-2006 were undiagnosed (prevalence in the U.S. - Goodarz et al. Popul Health Metr. 2009)
Health status - **Chronic kidney disease (CKD) – 23.5%**

- Diabetes 42.4% in participants with CKD,
- risk factors for diabetes included obesity - 44.0%;
- Hypertension - 80.5%;
- cardiovascular disease - 23.2%;
- family history of diabetes, 55.9%;
- dyslipidemia, 43.0%. (MacFarland et al. AM J Kidney Dis. 2011)
Medications – are the indications really „pure”

Which side we are patients or market?
Medications – are the indications really „pure”

Lipids - ↓ normative values inspite of progressive decrease of general health!

Blood pressure - stable normative values inspite of aging and increase of vessels stiffness!
7–29% of patients complain of statin-associated muscle symptoms (SAMS) (Stroes et al. Eur Heart J. 2015)

myopathy  3-5%  (Banach et al. Arch Med. Science, 2015)
Hypertension - Risk factor of falls and stroke

Fractures

- FSD
- SSMD
Genetics and muscle performance


Endurance and tolerance of exercises

myostatin, ADRB2, ADRB3, NPY, VDR, LPL, IGF 1, ACE

Muscle strength – myostatin, VDR, Col 1(α1), ACE
Epigenetics and muscle stem cells

Interplay between intrinsic and extrinsic factors

Autophagy – decisive stem-cell fate regulator fostering muscle regeneration in sarcopenia

Epigenetic impact on MyoD (master regulator of differentiation, directs of gen expression during skeletal myogenesis
Key points of mechanism of sarcopenia - the cells

- **Apoptosis**
  1. Extracellular,
  2. Mitochondrial,
  3. Endothelial reticulum
- **Autophagy**
- **Satellite cells proliferative potential**
Key points of mechanism of sarcopenia - muscle catabolism

- Autophagy
- calcium-activated proteases (calpain and caspases)
- ubiquitin-proteasome system (MuRF-1 and MAFbx ligases)
Key points - mechanism of sarcopenia

- Inflammation (TNF α, IL 6) → apoptosis, autophagy, ECM degradation – MMPs

- Hypoxia → apoptosis

- ROS (Mitochondria) → Apoptosis, autophagy

- UPR – apoptosis, autophagy
Mechanism of muscle satellite cell activation

[Charge and Rudnicki. Physiol.Rev. 2004]

Resting Satellite cell (Pax7)

HGF, FGF, Wnt7a →

Activated satellite cell (Pax7, Frizzeld7)

HGF, FGF, IGF I, Il-6, LIF → ≠ Myostatin, TGF-β

Proliferation of satellite cell (MyoD, Myf5, Pax7)

IGF I → New muscle fibre ≠ Myostatin, TGF-β

(Mrf4, myogenin)
Skeletal muscle hypertrophy and atrophy signaling pathways


IGF-1

- induction of protein synthesis
- block the ubiquitin-ligases MuRF1 and MAFbx by PI3K/Akt pathway [Trevor et al. Molecular Cell. 2004]

TNF alpha

- NF-kappaB-mediated upregulation of MuRF1 and MAFbx via p38 MAPK pathway
Mechanism of sarcopenia - neuromuscular junction


aging ↑ increase in oxidative stress (ROS)

mitochondria dysfunction

neuromuscular junction degeneration

progression of sarcopenia
Visceral fatt metabolic activity


visceral fatt

↑ resistin, leptin, **TNF-alfa**, IL-6, C-reactive protein, fibrinogen and plasminogen activator inhibitor 1 (PAI-1)
Chronic kidney disease

↑ Ubiquitin-Proteasome System and Myostatin

indoxyl sulfate → mitochondrial dysfunction
accelerates skeletal muscle atrophy

↑ IL-6, myostatin and atrogin-1 in the mice model of CKD mice → autophagya
Sarcopenia and structures involved by it

- Muscle fibres
- Neuromuscular junction
- Adipous tissue
- Fibrous tissue
- Artery network
Sarcopenia and cells involved by it

- Muscle fibre type I and II (a, b, x)
- Satellite cells
- Fibroblasts
- Adipocytes
- Nurons

- in spite of the progressive decline in muscle strength the capacity to produce eccentric torque is preserved in seniors
- eccentric training induce the multilevel muscle adaptations i.e. physiological, histochemical, metabolic, neural, cortical activity and stellite cel proliferation
- regular physical activity prevents the age-associated increase in muscle fat infiltration.
Exercises - current realistic targets of treatment

1. Strength of the atrophied muscle fibres
2. Interstitium volume hyperthrophy
1. Neuromuscular transmission
Sarcopenia


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Expected total muscle strength

1. Primary muscle strength (PMS)
2. Strength of the lost muscle fibres (SLMF)
3. Strength of the atrophied muscle fibres (SAMF)

\[ MS = PMS - SDMF - SAMF \]
Mechanism of sarcopenia

- ↑ intramuscular lipid content (CT) is associated with ↓ isokinetic strength

Exercises
Exercises - the older the better
Mr Rambo

24 70
FSD - Rotator cuff pathology - epidemiology


10% < 20 years

62% > 80 years

35% bilateral > 66 years

surgery > 250 000 per year in the USA
after 5 years muscle structural changes are irreversible
Rotator cuff tear and its muscles fate

**Tear** – atrophy, fibrosis, fatty infiltration (10% - 62%)

**Sarcopenia** – atrophy, fibrosis, fatty infiltration (13% - 50%)

**Metabolic syndrom** – atrophy, fibrosis, fatty infiltration (30% - 40%)
Morphometric changes of sarcopenic rotator cuff muscles


- muscle fibres atrophy
- infiltration by fatt cells
- increase of interstitial connective tissue – fibrosis
Supraspinatus disuse sarcopenia – morphometric prove of its reversibility

- **Experimental data**
  
  26% ↑ muscle fibres type I and II diameter


  partial reversibility of muscle atrophy


- **Clinical data MRI** - ↑ muscle volume


**Muscle strength**
- ↓ 48,2% after 6 weeks/ FD 1,85
- ↓ 65,5% after 12 weeks/ FD 2,28
- ↓ 67,3% after 24 weeks/ FD 2,43

**Interstitium volume**
- control - 2,9 %
- 6 weeks - ↑ 13,3%
- 12 weeks - ↑ 21,2%
- 24 weeks - ↑ 22,26%
- 24 weeks after reconstruction - ↓ 4,6%
SSDM of rotator cuff - supraspinatus atrophy is reversible

- **Experimental data**
  
  26% ↑ muscle fibres type I and II
  

- **Partial reversiblity of muscle atrophy**
  

- **Clinical data ↑ muscle volume 11.3%**
  

If neuromuscular transmission is normal (SFEMG) than

Muscle fibres type I and II atrophy – reversible

Interstitium volume hypertrophy – partially reversible

If neuromuscular transmission is normal (SFEMG) than

1% ↓ Muscle fibre II diameter → ↑ 0,93%
Interstitium volume

1% ↑ Muscle fibre II diameter/ → ↓ 0,62
Interstitium volume
Sarcopenia - current limits of its reversibility

1. Sarcopenia is not as important as its fundamental modulators
2. Think about the key functional sarcopenic deficits
3. Search for selective sarcopenic deficits
4. Keep foot stability - insols
5. Thinking about them means we can at least partially stop progression or reverse the sarcopenic changes