Age-related muscle weakness

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Who am I?

Muscular Pathophysiology Group
The bigger picture…
Life Expectancy at Birth

![Graph of Life Expectancy at Birth](image)
Percentage of under 16 to over 65
Incidence of Falls per 100,000 population increases rapidly with increasing age.
Sarcopenia – A problem for all.

Clarence Bass
Data courtesy of Prof A. Young

World Masters Weightlifting Championships 1999
Men (<85 kg)

Best lift (kg)

Clean & Jerk
Snatch

Age group (years)

35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85+
Data Courtesy of Prof A Young

Cross sectional CT scan of upper thigh from healthy 20 year old female

Cross sectional CT scan of upper thigh from healthy 80 year old female
'As we age our muscles become smaller and weaker'

Redrawn from Lexell et al., 1983
Why do aged muscles weaken?

• Million dollar question and this is what our group has been interested in for a number of years.

• Malcolm Jackson – Free radical theory
  • Anne McArdle – originally a postdoctoral fellow with RIA and now a professor holding RIA programme grant investigated protective proteins.
  • Graeme Close – Insulin resistance
Ageing results in an increased production of free radicals
What are Free radicals – I will let ‘M’
tell you
Denaturation

Peroxidation

Lipids

R

Enzymes

R

Proteins

R

Nucleic acids

R

Inactivation

Modification
...but can increased free radical production result in losses of muscle mass and function?

Muscles that have been modified to produce increased free radicals

Vasilaki et al
Muller et al., 2006
Aged muscle fails to produce protective proteins

- Aged muscle produces increased free radicals but how does this lead to accelerated ageing of skeletal muscles?
- Number of suggestions but one that we have given a great deal of attention to is the role of protective proteins, known as heat shock proteins (HSPs).
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DAMAGING STRESS

UNSTRESSED CELL
CORRECTLY FUNCTIONING PROTEINS
Resting level of HSPs

MILD STRESS

INCREASED CONTENT OF HSPs

DAMAGING STRESS

STABILIZATION OF CELLULAR PROTEINS AND PROTECTION AGAINST DAMAGE

McArdle et al., 2002
• Adult muscle adapts following exercise by the increased production of Heat Shock Proteins (HSPs).
• This increased content of HSPs has been shown to protect muscles from damage following contractile activity.
• Ageing attenuates HSP induction following exercise.

* P<0.05 compared with adult non-exercised value

Vasilaki et al. (2002)
We are attempting to correct this

- Genetic approaches
- Drugs
- Exercise (short and long term)
Specific Force

McArdle et al., 2004, FASEB J
Maximum Force

McArdle et al., 2004, FASEB J
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New hypothesis

Ageing $\rightarrow$ Increased ROS $\rightarrow$ Insulin Resistance (Hyperinsulinaemia)

- Impaired Insulin signaling
  - Decreased Protein Synthesis
  - Increased protein breakdown

- Decreased Muscle Mass (Size & Number)
  $\rightarrow$ Loss of muscle function

Attenuated HSP responses and damage to contractile proteins

Weakening of muscle fibres
Ageing results in insulin resistance.
Insulin

IRα-IRβ
IRb-α IRb-β

IRS-1

Glucose

Glucose

Protein Synthesis

PI-3K

PI-3K

Phosphorylated AKT

AKT

mTOR

Atrogin-1

Protein Degradation

Atrogenes

GLUT 4

Vesicle

Glycogen

Foxo phosphorylated (Remains in cytoplasm preventing atrophy)
Latest studies

• Correct insulin resistance using:
  • Drugs (Metformin, rosiglitazone, resveratrol, rosuvastatin).
  • Prolonged exercise
  • Investigate early correction of insulin resistance on loss of muscle mass and function.
• These studies are part of my RIA fellowship plus my first PhD student.
Lets finish on a high!

Age-related muscle weakness is not completely beyond our control
Whitlock’s 2:54:49 time puts him in the top one percent of marathon runners. At New York, only 480 runners bettered three hours.

“People under-estimate what old people can accomplish, old people are the worst in that respect. They let themselves be inhibited by age.” Ed Whitlock 2005

I started training at 72 when I found myself looking, feeling and acting old. It not only improved my physique, but gave me a healthy perspective on life. I am here to tell you that the myth that we should surrender to old age accepting inabilities which we are told are inevitable, is dead wrong.
Musculoskeletal Achievements of the over 70’s

Payton Jordan March 19 1917

Graeme Close May 8 1977
Who knows what 3 years might bring…
Body composition when there is a defect in insulin receptors

**Table 2**

Body composition in the control and MIRKO mice

<table>
<thead>
<tr>
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<th>Tissue mass</th>
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<tr>
<td></td>
<td>Gastrocnemius and quadiceps muscles</td>
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<tr>
<td>n</td>
<td>(mg)</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
</tr>
<tr>
<td>MIRKO</td>
<td>8</td>
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\(^A\)P < 0.05 versus control group by two-tailed t test. EDL, extensor digitorum longus; BW, body weight.

*Kim et al., 2000*