Healthy ageing

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Content

What is healthy ageing? Different angles.

Some hypotheses.

Ageing muscle.

Take home messages.

What is healthy ageing?

Any ideas?

What is healthy ageing? Anti-ageing?

- Definition is difficult
- Looking healthy?
- Feeling young?
- Is anti-ageing about prolonging your life?
  - Avoiding an “early” death?
  - Is anti-ageing actually anti-dying?

Some Hollywood tips

- Drink a lot of water
- Get a lot of sleep
- Always wash your make-up of before bed
- Don’t smoke and low alcohol intake
- Try not to stress
- Wear sunscreen
- Lots of fruit and vegetables
- Moisterize your skin
- Exercise often

Classic Hollywood anti-ageing therapy

- Hormone Replacement Therapy
- Menopause
- Low T and Male Menopause
- Nutrition and Fitness
- Nutritional Supplements
- Lifestyle Management
- Stress Management
- Brain Balancing
- Weight Management
- Non-Surgical Facial and Body Rejuvenation Procedures

- Cosmetic Surgery

More unconventional

- Tailored breast implants
- Threadlifts for butts and boobs
- An injectable for the eye area
- Chemically dissolve cellulite
- 'Nanotechnology' hair conditioning
- 'Lip gloss in a syringe'
- A new vitamin for thinning hair
- Facial that uses 3D printing technology
- Permanent camouflage for stretch marks and scars
- Plastic bristles, not microneedles, to push anti-wrinkle product into skin
- A chin strap that superpowers lifting facials
- Magnetic resonance for new kind of beauty rest

Old wine in new bottles?

So far, there are three types of anti-ageing

- 'Hollywood' style: which is more about *looking* younger
- 'Healthy' ageing: exercise, nutrition; which is more about preventing decline
- 'Experimental'

Experimental anti-ageing

Telomerase therapy

- 2004 review: doubts
  - does it really affect organismal ageing
  - may promote tumorigenesis
- 2016 review: ‘experiments in cell and animal models provide proof of concept’

=> Not much progress if you ask me

Experimental anti-ageing

Stem cell therapy (SCT), research started +/- 1981

=> Still a lot of problems to overcome, but hopeful

Ageing population => more medical conditions that may benefit from SCT

Embryonic stem cell therapy applications for autoimmune, cardiovascular, and neurological diseases: A review. Edgar et al, 2018.

=> Still a lot of problems to overcome, but hopeful

We'll stop here

Let's look at it from another angle

Theories of ageing

- Free Radical Theory
- The Neuroendocrine Theory
- Telomerase Theory of Aging
- The Wear and Tear Theory
- The Rate of Living Theory
- The Waste Product Accumulation Theory
- The Cross-linking Theory
- The Immune Theory
- Theories of Errors and Repairs
- The Order to Disorder Theory

Theories of ageing

Some of these contradict and others overlap.

But underlying these are three main biochemical processes involved in aging

- Oxidation
- Glycation
- Methylation

Other relevant processes are chronic inflammation and hormonal deregulation.

Anti-aging medicine, Arora et al, 2008.

Oxidation

- Free radicals miss an electron, making them unstable
- Free radicals in small and controlled quantities are useful in everyday metabolism.
- Free radicals damage the cell membrane which is composed of lipids and proteins.
- Their interaction results in the production of the chemical melondialdehyde which is very harmful, contributing to another important aging process called glycation.

Glycation

- When glucose molecules and other sugars such as fructose attach themselves to proteins, it is called glycation.
- The binding of sugar to protein causes cross linking of proteins.
- Cross linked proteins cause more damage by reacting with free radicals and other toxins to create Advanced Glycation Endproducts (AGEs).
- These AGEs bind to cells at special attachment sites called RAGEs (Receptor for AGEs).
- Glycation also affects DNA. A cross linked DNA molecule is of no use at all.

Methylation

- Methylation is adding ‘methyl groups’ on proteins, DNA and other molecules to keep them in good, active condition.
- This is necessary for the **normal maintenance of tissues** and is usually kept at a healthy levels naturally by the body.
- Methylation of certain parts of the DNA causes **permanent switching off of unnecessary genes** and saves the body from abnormal DNA division.
- This means that methylation of those particular sections of DNA blocks any abnormal DNA from being passed onto the future generations of cells.

Methylation

- Any **chronic inflammation process affects methylation** because the immune system, which is heavily involved in fighting inflammation, gorges itself on methyl groups, leaving nothing for other tissues of the body.

- Low methylation is reflected in the increasing levels of homocysteine, which is found in chronic inflammatory processes such as lupus, heart disease and diabetes.

- Increased intake of methylators reduces the risk of these diseases.

We'll stop here again

Let's look at it from yet another angle

Top Causes of Death (USA, 2010)

Number of deaths for leading causes of death

- Heart disease: 611,105
- Cancer: 584,881
- Chronic lower respiratory diseases: 149,205
- Accidents (unintentional injuries): 130,557
- Stroke (cerebrovascular diseases): 128,978
- Alzheimer's disease: 84,767
- Diabetes: 75,578
- Influenza and Pneumonia: 56,979
- Nephritis, nephrotic syndrome, and nephrosis: 47,112
- Intentional self-harm (suicide): 41,149

Of course, this is in how far one really knows the cause of death!

But, do we have a winner?

- Conventional medicine: 783,936 per year
  - adverse reactions to prescribed drugs: 2.2 million per year
  - antibiotics for viral infections: 20 million per year
  - unnecessary medical and surgical procedures performed: 7.5 million per year
  - people exposed to unnecessary hospitalization annually: 8.9 million per year
- Psychiatric drugs kill more than half a million people every year among those aged 65 and above in the USA and Europe.

So, what is anti-ageing?

- Anti-ageing is about prolonging your life
  - avoid an early death?
  - anti-ageing is anti-dying?

- This perhaps means that at this moment, we can try to postpone the moment of expected death, but not indefinitely.

- ‘True anti-ageing’ is simply … not ageing, but how would that work?

So, what is anti-ageing?

- If it is about prolonging your life, it means optimal ageing
- Each organ system should be supported
- Until now, it remains easy
  - Eating a correct diet
  - Improve physical exercise performance, which includes aerobic, anaerobic and flexibility training

Optimal ageing

Rank	Name	Sex	Birth date	Age as of 24 May 2023	Country of residence
1	Maria Branyas[4]	F	4 March 1907	116 years, 81 days	Spain[c]
2	Fusa Tatsumi[4]	F	25 April 1907	116 years, 29 days	Japan
3	Edie Ceccarelli[4]	F	5 February 1908	115 years, 108 days	United States
4	Tomiko Itooka[4]	F	23 May 1908	115 years, 1 day	Japan
5	Inah Canabarro Lucas[4]	F	8 June 1908	114 years, 350 days	Brazil
6	Hazel Plummer[4]	F	19 June 1908	114 years, 339 days	United States
7	Ushi Makishi[4]	F	15 February 1909	114 years, 98 days	Japan
8	Juan Vicente Pérez[4]	M	27 May 1909	113 years, 362 days	Venezuela
9	Elizabeth Francis[4]	F	25 July 1909	113 years, 303 days	United States
10	Ethel Caterham[4]	F	21 August 1909	113 years, 276 days	United Kingdom

Optimal ageing: pattern?

Rank	Name	Sex	Birth date	Death date	Age	Country of death or residence
1	Jeanne Calment	F	21 February 1875	4 August 1997	122 years, 164 days	France
2	Kane Tanaka[6]	F	2 January 1903	19 April 2022	119 years, 107 days	Japan
3	Sarah Knauss[7]	F	24 September 1880	30 December 1999	119 years, 97 days	United States
4	Lucile Randon[4]	F	11 February 1904	17 January 2023	118 years, 340 days	France
5	Nabi Tajima[6]	F	4 August 1900	21 April 2018	117 years, 260 days	Japan
6	Marie-Louise Meilleur[8]	F	29 August 1880	16 April 1998	117 years, 230 days	Canada
7	Violet Brown[6]	F	10 March 1900	15 September 2017	117 years, 189 days	Jamaica
8	Emma Morano[6]	F	29 November 1899	15 April 2017	117 years, 137 days	Italy
9	Chiyo Miyako[9]	F	2 May 1901	22 July 2018	117 years, 81 days	Japan
10	Delphia Welford[10]	F	9 September 1875	14 November 1992	117 years, 66 days	United States

Cause of death

- If they lived this long, why do they die?
- Many report state ‘Advanced age’…
- I did not find one supercentenarian die in a motorcycle accident!
- So which theory is correct?

Theories of ageing

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Theories of ageing

Is it a ‘fade out scenario’?

Many 100+ are cognitive (relatively) ok

As far as we know, no major heart/long/kidney problems

But all are devoid of functionality

So what organ are we missing?

Ageing

Many physiological changes in all organ systems:

- Cardiovascular: cardiac output ↓, blood pressure ↑
- Pulmonary: ↓ gas exchange, ↓ vital capacity
- Renal: clearance ↓
- Gastro-intestinal: ↓ motility
- Skin: generalized atrofy, ↓ collagen/elastin
- Musculoskeletal: osteoporosis

→ What with muscle itself?

Ageing muscle

Biggest organ (40% of body weight)

Function

- Locomotor
- Hormonal (insulin)
- Deposit of nutrients (glycogen, proteins, fat)

Influences many other organ systems

Hypothesis

Muscle ageing is the default ageing process

All other decline is just bad habits, bad luck or bad genes

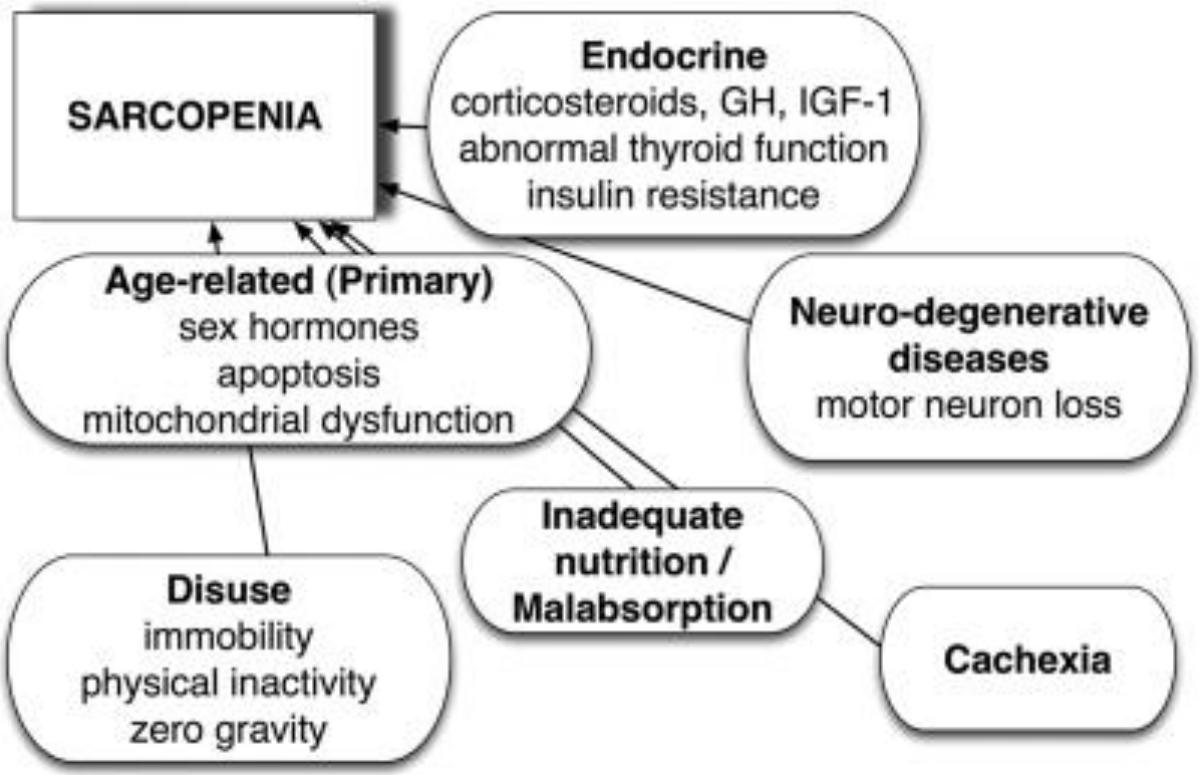
Sarcopenia: definition

- ‘Sarx’ (meat) and ‘penia’ (loss, shortage)

- Muscle mass diminishes by
  - 1-2% a year (>50 year old)
  - 1.5-3% a year (>60 year old)
  - Even increased decline afterwards (>70 year old)

- Definition (EWGSOP):
  - 2010: age-related decline of muscle mass, strength and function
  - 2018: sarcopenia is a progressive and generalised skeletal muscle disorder, with a decline in strength, mass and function

Etiology



Sarcopenia: European consensus on definition and diagnosis. EWGSOP. Age and Ageing 2010; 39: 412–423.

Hypothesis

If exercise increases the neural drive

That means that exercise increases neuron activity and stimulates regeneration

Is the initial decline of neurons the cause of sarcopenia?

Or is disuse of muscle the cause of neuron degeneration?

Why some people with brain markers of Alzheimer's have no dementia

- “Nerve cells can't communicate because of the buildup of toxic proteins that disrupt synapse.”
- Resilient individuals had a unique synaptic protein signature that set them apart from both demented AD patients and normal subjects with no AD pathology.
- “Synaptic resistance to amyloid beta and tau.”

Olga Zolochevska, Nicole Bjorklund, Randall Woltjer, John E. Wiktorowicz, Giulio Taglialatela. Postsynaptic Proteome of Non-Demented Individuals with Alzheimer’s Disease Neuropathology. *Journal of Alzheimer's Disease*, 2018

Exercise and Alzheimer's

- **Improvements in** some cognitive components such as sustained **attention**, visual **memory**, and frontal cognitive **function** in patients with AD.

What are the Benefits of Exercise for Alzheimer's Disease? A Systematic Review of the Past 10 Years. 2015.

- Exercise appears to improve brain blood flow, **increase hippocampal volume**, and **improve neurogenesis.**
  Exercise as a treatment for AD shows improvement in cognitive function, decreased neuropsychiatric symptoms, and a slower decline in activities of daily living (ADL).
  Exercise has been shown to have fewer side effects and better adherence compared to medications.

Alzheimer's Disease and Exercise: A Literature Review. 2018.

Muscle ageing: primary sarcopenia (PS)

Multifactorial cause

- Changes in muscle architecture
  - Muscle fiber characteristics => US course
  - Muscle tissue composition
- Neuronal changes
  - Central activation
  - Spinal properties
  - Motor unit and neuromuscular junction
- Hormonal factors

Muscle composition: tendons

The structure and composition of tendons are important for **optimal force transfer** and function.

Tendon stiffness affects the time required to stretch the elastic component and will **influence the rate of force development**.

Age-related changes: collagen concentration decreases and extracellular matrix components (proteoglycans, glycosaminoglycans) increase.

In elderly, a training-induced **increase in fiber length is compensated by an increase in tendon stiffness.** This enables the fibers to maintain their operational range within the optimal region of the length-tension and force-velocity relationships. The exact relation of these changes in tendons are still unclear due to conflicting data.

Muscle composition: muscle tissue

Force transmission can be generated in two ways: longitudinal and lateral.

The longitudinal force transfer from fiber to myotendineous junction creates a change in the force development rate and the power by changing the proteins-to-fiber ratio.

The lateral force transfer uses **costameres** - large membrane-cytoskeletal complexes - that couple the intracellular-extracellular matrix to transfer up to 80% of the force.

As **costameres are lost during aging** also an important transfer mechanism fails.

Calcium reuptake is reduced with ageing, due to a loss of specific (ryanodine/dihydropyridine) receptors. This leads to a **weaker excitation-contraction** coupling and to a **lessened motor coordination / task performance** and a **higher rate of muscle fatigue**.

Muscle composition: vascular tissue

There is an overall reduction in blood flow and oxygen delivery with age

- structural alterations in the vasculature
- increased muscle sympathetic outflow
- balance alterations in locally formed vasodilators/vasoconstrictors.
- maximal cardiac output decreases with age
- this decrement in central capacity also affects peripheral blood flow
- number of muscle capillaries was shown to dramatically decrease with age
- remaining capillaries are separated from their muscle fibers due to the increase in connective tissue

Muscle composition: vascular tissue

What else? Ageing is associated with

- a lower hemoglobin and arterial oxygen content
- a greater metabolic cost of contraction
- excessive energy demand from ion pumping

This results in a reduced muscle efficiency and function.

In parallel with the reduced oxygen uptake, release of lactate was increased in the sedentary elderly, indicating that **anaerobic metabolism was increased to compensate for the lower oxidative metabolism**.

Muscle composition: adipose tissue

In the ageing skeletal muscle, **elevated adipose deposition** is observed at both inter- and intramuscular sites.

The exact reason is unknown, but **lipid accumulation in muscle correlates with a lower mitochondrial function**.

This could explain why an **increased ectopic muscle adiposity** and total body adipose tissue **negatively impacts strength, power and torqu**e.

A higher **muscle tissue fat content negatively affects performance**.

Muscle composition: mitochondriae

Mitochondria are responsible for energy production and are involved in apoptosis, calcium buffering, synaptic transmission and redox-regulation.

They are abundantly present in pre- and postsynaptic end plates and are critical in neuromuscular junction (NMJ) functioning.

Mitochondrial abnormalities have been implicated in the pathogenesis of musculoskeletal ageing.

Because of **aberrant mitochondrial redox homeostasis**, there is a failure to upregulate anti-oxidative enzymes. This results in an **increased oxidative stress** and impairs the ability of the muscle to properly adapt to acute/chronic stress.

Hypothesis

Mitochondrial dysfunction could be the key to ageing

Neuronal factors

Neuronal factors have an important effect on the mass-strength relationship, some studies state up to 50%.

Changes are seen

- on a central level
- at the spinal cord
- in the motor unit (MU)
- at the neuromuscular junction (NMJ)

Neuronal factors: central activation

Ageing results in

- cortical atrophy
- altered neurochemistry
- reduced motor cortical excitability
- altered agonist-antagonist co-activation strategies

This leads to **11% reduction in motor performance** and in voluntary activation capacity.

Morphometric changes in the motor cortex due to ageing include a **43% volumetric reduction** in the premotor cortex neuron size.

Elderly individuals **lose** on average **45% of their total myelinated nerve fiber length**.

Neuronal factors: central activation

Impaired neurotransmission is responsible for some age-related abnormalities including serotonergic, cholinergic, adrenergic, dopaminergic, GABA-ergic and glutaminergic systems.

Ageing also decreases cortical excitability and reduces cortical plasticity.

In the muscle **agonist-antagonist co-activation** strategy

- impaired activation of the former
- increased co-activation of the latter
- leads to a smaller and slower force production

Neuronal factors: spinal properties

Each motor neuron typically has 50.000 synapses to convey commands.

There is a 37% decline in unmyelinated fiber density.

There is a 38% decline in myelinated fiber density.

This is in part responsible for the 8–18% age-related decrease in nerve conduction velocity.

Neuronal factors: motor unit (MU)

A MU is the combination of a motor neuron and all the muscle fibers it innervates.

Each MU accounts for the innervation of 100-10.000 muscle fibers, depending on the physiological role of the muscle.

MUs demonstrate numerous age-related adaptations, including changes in

- morphology
- behavior
- electrophysiology

Motor neuron degeneration and consequent denervation of myofibers are also a major cause of muscle mass loss.

Neuronal factors: NMJ

Changes in NMJ morphology depend on muscle type and include variation of the nerve terminal area size, the end plate size, the number of synaptic vesicles and in the content of mitochondria.

The ageing NMJ exhibits elevations in presynaptic nerve terminal branching and in post-synaptic distribution of receptor sites for neurotransmitters. **Disuse further compounds these changes**.

These effects seem to appear first in the postsynaptic region, suggesting that **the degeneration process begins with the myofiber** before progressing up to the presynaptic nerve terminals.

Hypothesis

So sarcopenia seems to be more than muscle alone

But the vicious circle starts within the muscle, probably following disuse

So ageing starts with disuse (days like today)

Take home messages

Think about what anti-ageing means to you

Anti-ageing perhaps means anti-muscle decline

Muscle decline might be the mediator of age-related diseases