DR. HYMAN+

Nutrition and Optimal Aging: Mastering Nutrient Demands of Aging

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Presentation Outline

- Background and “hallmarks of aging”
- Primer on nutrients
  - Macronutrients, vitamins, minerals, non-essential nutrients
  - Dietary Reference Intakes
- Why nutrient demands increase with age
  - Physiology, lifestyle, social factors, medications
  - “Triage theory”
  - Nutrition and hallmarks of aging – specific foods & nutrients

Presentation Outline

- Specific nutrients of interest
  - Protein
    - Measures of quality, bioavailability, amino acids of interest
    - mTor
  - Vitamins, minerals, essential nutrients
    - Vitamin B_{12} ,vitamin D, calcium, magnesium, iron, choline
  - Other nutrients of interest
    - Creatine, NAD+ precursors

- Summary

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Serum vitamin E concentrations among highly functioning hip fracture patients are higher than in nonfracture controls

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Serum Vitamin E Concentrations and Recovery of Physical Function During the Year After Hip Fracture

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Original article

Higher serum concentrations of dietary antioxidants are associated with lower levels of inflammatory biomarkers during the year after hip fracture

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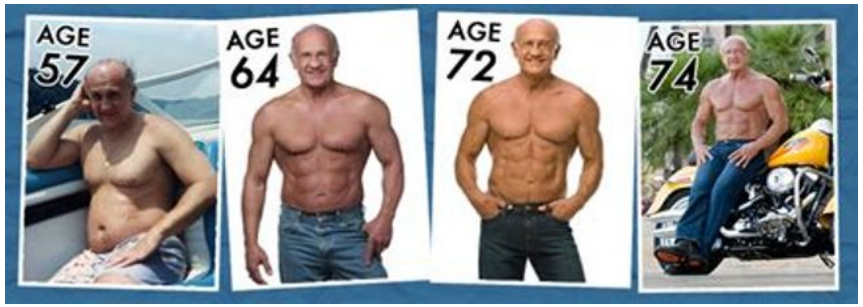
Validated Living Worldwide Supercentenarians 113+, Living and Recently Deceased: February 2022

Robert D. Young*

By definition, a validated supercentenarian is a properly documented centenarian who has lived to be at least the age of 110 years. Tables 1 and 2, based on records maintained by members of the Gerontology Research Group (GRG), continue the series last published in *Rejuvenation Research* in 2021—giving the latest list of living supercentenarians, currently with a cutoff age of 113+. It should be emphasized that this list does not include *all* living supercentenarians, only those whose claim can be validated to the required standard as well as trimmed to 113 and over; the true population is estimated to be in the region of 800–1000 (worldwide). For more details or to support GRG's work, please contact them at www.grg.org. As of January 26, 2022, there were 23 living supercentenarians on our list (all females).



Cell

Leading Edge
Review

The Hallmarks of Aging

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Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Aging research has experienced an unprecedented advance over recent years, particularly with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution. This Review enumerates nine tentative hallmarks that represent common denominators of aging in different organisms, with special emphasis on mammalian aging. These hallmarks are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A major challenge is to dissect the interconnectedness between the candidate hallmarks and their relative contributions to aging, with the final goal of identifying pharmaceutical targets to improve human health during aging, with minimal side effects.

Lopez-Otin et al. (2013) *Cell* 153, 1194–1217.

Cell
Leading Edge

CellPress

Review

Hallmarks of aging: An expanding universe

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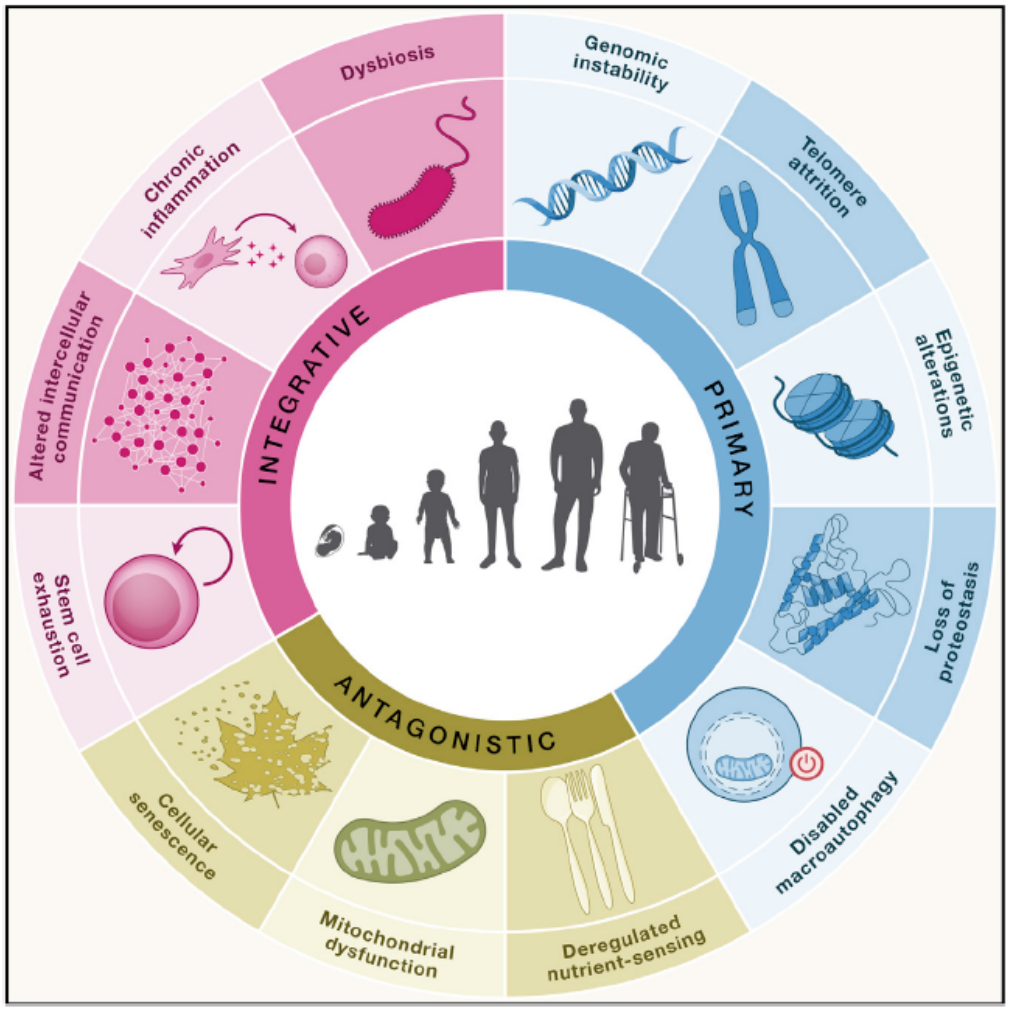
https://doi.org/10.1016/j.cell.2022.11.001

SUMMARY

Aging is driven by hallmarks fulfilling the following three premises: (1) their age-associated manifestation, (2) the acceleration of aging by experimentally accentuating them, and (3) the opportunity to decelerate, stop, or reverse aging by therapeutic interventions on them. We propose the following twelve hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. These hallmarks are interconnected among each other, as well as to the recently proposed hallmarks of health, which include organizational features of spatial compartmentalization, maintenance of homeostasis, and adequate responses to stress.

Lopez-Otin et al. (2023) *Cell* 186(2):243-278.


Dysbiosis
Genomic instability
Telomere attrition
Epigenetic alterations
Loss of proteostasis
Disabled macroautophagy
Deregulated nutrient-sensing
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Altered intercellular communication
Chronic inflammation
INTEGRATIVE
PRIMARY
ANTAGONISTIC

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Review

Hallmarks of Health

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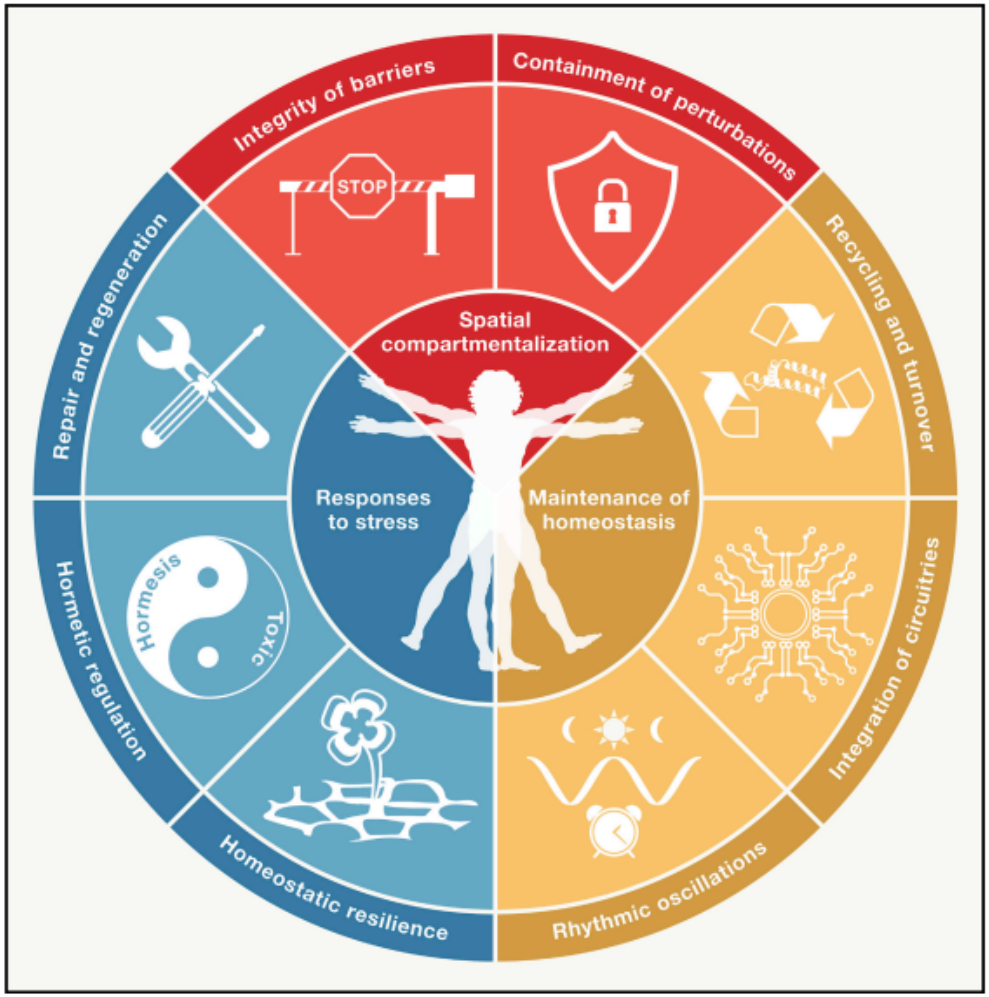
https://doi.org/10.1016/j.cell.2020.11.034

SUMMARY

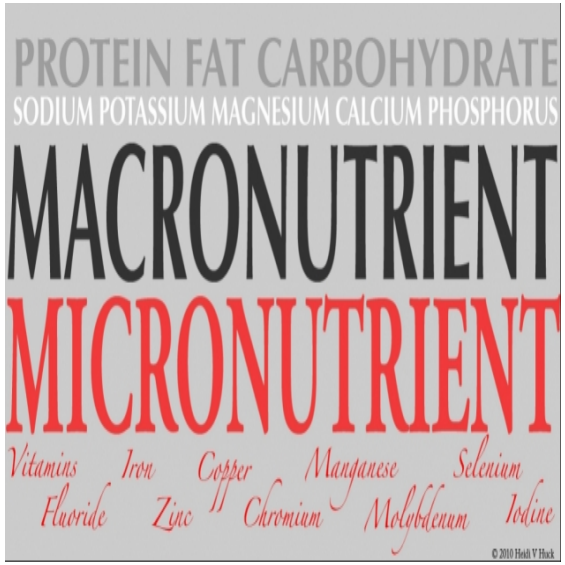
Health is usually defined as the absence of pathology. Here, we endeavor to define health as a compendium of organizational and dynamic features that maintain physiology. The biological causes or hallmarks of health include features of spatial compartmentalization (integrity of barriers and containment of local perturbations), maintenance of homeostasis over time (recycling and turnover, integration of circuitries, and rhythmic oscillations), and an array of adequate responses to stress (homeostatic resilience, hormetic regulation, and repair and regeneration). Disruption of any of these interlocked features is broadly pathogenic, causing an acute or progressive derailment of the system coupled to the loss of numerous stigmata of health.

Lopez-Otin et al. (2021) *Cell* 184(1):33-63.


Integrity of barriers
Containment of perturbations
Recycling and turnover
Integration of circuitries
Rhythmic oscillations
Homeostatic resilience
Hormetic regulation
Repair and regeneration
Spatial compartmentalization
Responses to stress
Maintenance of homeostasis
STOP
Hormesis
Toxic

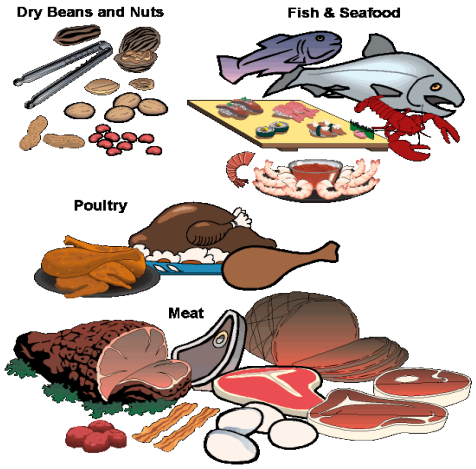
Nutrients: Overview

- Three macronutrients
  - Protein
    - 4 calories per gram
  - Carbohydrate
    - 4 calories per gram
  - Fat



Macronutrients: Protein

- Sources
  - Meat, eggs, dairy, beans, etc.
- Types
  - Complete proteins
    - Contain all 9 essential amino acids (EAA)
      - Body cannot produce EAA's
    - Most animal proteins complete
  - Incomplete proteins
    - Do not contain all 9 EAA's
    - Most plant proteins incomplete, can be combined to become complete
- Digestion and Absorption
  - Broken down to amino acids by protease enzymes
  - 4 calories per gram



Macronutrients: Carbohydrate

- Sources
  - Grains, vegetables, fruit, bread, etc.
  - No essential carbohydrates
- Types
  - Sugar
    - “Simple” or “Complex” - monosaccharide or disaccharide
  - Starch
    - “Complex” - polysaccharide
  - Fiber
    - Non-starch polysaccharides
    - Soluble vs. insoluble
- Digestion and Absorption
  - Broken down to glucose (except fiber) by amylase enzyme
  - 4 calories per gram

Macronutrients: Fat

- Sources
  - Nuts, oils, avocadoes, animal foods
  - Two essential fatty acids (EFA's)
    - Alpha linolenic acid (omega-3) & linoleic acid (omega-6)
- Types
  - Saturated: all carbon-carbon bonds
    - Meat, dairy, coconut, palm, cocoa
  - Monounsaturated: one carbon=carbon bond
    - Vegetables, nuts
  - Polyunsaturated: multiple carbon=carbon bonds
    - Fish, vegetables, nuts
- Digestion and Absorption
  - Broken down to fatty acids by lipase enzyme
  - 9 calories per gram

Micronutrients: Vitamins

- Vitamins
  - 13 organic (contain carbon) compounds essential to health
    - Vitamin A (retinol… *not* beta-carotene), B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5, B_6, B_7 (biotin), vitamin B_9 (folic acid), vitamin B_{12}, vitamin C, vitamin D, vitamin E, vitamin K
  - No endogenous production… must be obtained through diet
  - ex.) Vitamin K
    - Allows blood to coagulate normally, involved in bone formation and strength, prevents calcification of arteries and heart disease

World's Healthiest Foods rich in vitamin K

Food	Cals	%Daily Value
Kale	36	1327.6%
Spinach	41	1110.6%
Collard Greens	49	1045%
Swiss Chard	35	715.9%

Vitamin K_2

Micronutrients: Minerals

- Minerals
  - 16 inorganic (no carbon) compounds essential to health
    - Macro - calcium, phosphorus, potassium, sodium, chloride, magnesium, sulfur
    - Trace - iron, iodine, zinc, chromium, selenium, fluoride, molybdenum, copper, manganese
  - No endogenous production… must be obtained through diet
  - ex.) Calcium
    - Bone formation, proper function of nervous, muscular, endocrine systems

World's Healthiest Foods rich in calcium

Food	Cals	%Daily Value
Yogurt	154	44.8%
Tofu	86	39.6%
Sesame Seeds	206	35.1%
Sardines	189	34.6%
Milk - Goat	168	32.6%
Collard Greens	49	26.6%
Spinach	41	24.4%
Cheese	72	22.1%
Turnip Greens	29	19.7%
Cow's milk, grass-fed	74	13.7%

Micronutrients: Non-essential

- Non-essential micronutrients
  - Not "essential"… but *many* health benefits
  - Carotenoids
    - Lutein, zeaxanthin, lycopene, α- & β-carotene, etc.
  - Flavonoids
    - Resveratrol, curcumin, EGCG, anthocyanidins, etc.







  - Choline, creatine, l-carnitine, coenzyme Q_{10}



Nutrients: Reference Values

- Nutritional Reference Values
  - 1997 Dietary Reference Intakes (DRI)
    - *Recommended Dietary Allowances (RDA)*
    - *Tolerable Upper Levels (UL)*
    - Estimated Average Requirement (EAR)
    - Adequate Intakes (AI)

- Recommended Dietary Allowances (RDA)
  - Information on food labels
  - Average daily dietary intake sufficient enough to meet nutrient requirements of 97– 98% of healthy people
  - Varies by gender and life-stages (pregnancy, age, etc.)
  - Prevent nutrient deficiency diseases… not chronic disease

Nutrients: Reference Values

- Tolerable Upper Intake Level (UL)
  - Highest level of daily nutrient intake that will not pose a risk of adverse effects in healthy people
    - Highly conservative… substantial margin for error

- Evidence-base for DRI values needs improvement
  - Often based on old studies (1960's) and few RCT's
    - *2008 Institute of Medicine: The Development of DRIs 1994–2004*
  - Many argue RDA's far too low
    - Vitamin D – 2010 *Journal of Nutrition*
    - B-vitamins – 1996 *Journal of American Geriatrics Society*
    - Vitamin C – 1994 *Journal of American Medical Association*

Nutrients: Reference Values

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (µg/d)[a]	Vitamin C (mg/d)	Vitamin D (µg/d)[b,c]	Vitamin E (mg/d)[d]	Vitamin K (µg/d)	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin (mg/d)[e]	Vitamin B_6 (mg/d)	Folate (µg/d)[f]
Infants										
0 to 6 mo	400*	40*	10	4*	2.0*	0.2*	0.3*	2*	0.1*	65*
6 to 12 mo	500*	50*	10	5*	2.5*	0.3*	0.4*	4*	0.3*	80*
Children										
1–3 y	300	15	15	6	30*	0.5	0.5	6	0.5	150
4–8 y	400	25	15	7	55*	0.6	0.6	8	0.6	200
Males										
9–13 y	600	45	15	11	60*	0.9	0.9	12	1.0	300
14–18 y	900	75	15	15	75*	1.2	1.3	16	1.3	400
19–30 y	900	90	15	15	120*	1.2	1.3	16	1.3	400
31–50 y	900	90	15	15	120*	1.2	1.3	16	1.3	400
51–70 y	900	90	15	15	120*	1.2	1.3	16	1.7	400
> 70 y	900	90	20	15	120*	1.2	1.3	16	1.7	400
Females										
9–13 y	600	45	15	11	60*	0.9	0.9	12	1.0	300
14–18 y	700	65	15	15	75*	1.0	1.0	14	1.2	400[f]
19–30 y	700	75	15	15	90*	1.1	1.1	14	1.3	400[f]
31–50 y	700	75	15	15	90*	1.1	1.1	14	1.3	400[f]
51–70 y	700	75	15	15	90*	1.1	1.1	14	1.5	400
> 70 y	700	75	20	15	90*	1.1	1.1	14	1.5	400
Pregnancy										
14–18 y	750	80	15	15	75*	1.4	1.4	18	1.9	600[f]
19–30 y	770	85	15	15	90*	1.4	1.4	18	1.9	600[f]
31–50 y	770	85	15	15	90*	1.4	1.4	18	1.9	600[f]
Lactation										
14–18 y	1,200	115	15	19	75*	1.4	1.6	17	2.0	500
19–30 y	1,300	120	15	19	90*	1.4	1.6	17	2.0	500
31–50 y	1,300	120	15	19	90*	1.4	1.6	17	2.0	500

Nutrients: Reference Values

- Remember the following about RDA
  - Amounts to prevent nutrient deficiency diseases…
    not optimal thresholds to protect against chronic diseases
  - Reading labels simply a guide… based on recommendations for young adult women (2,000 kcal)

- Nutritional needs not “one size fits all”
  - Nutrient needs vary between people (gender, weight, etc.)
    - Areas not addressed by DRI’s… physical activity, smoking, etc.
  - Nutrient needs vary by stage of life (age, pregnancy, etc.)
    - Areas not addressed by DRI’s… before/during disease, stress, etc.
  - *Especially important to older adults with varying comorbidities*

Why nutrient demands increase with aging

Multifactorial Roots

- "Meals on Wheels"
  - **M**edications
  - **E**motional problems
  - **A**norexia or alcoholism
  - **L**ate-life paranoia
  - **S**wallowing disorders
  - **O**ral problems
  - **N**o money
  - **W**andering (sign of dementia)
  - **H**yperthyroidism
  - **E**nteric problems (malabsorption)
  - **E**ating problems (cannot self feed)
  - **L**ow-salt, low-cholesterol diets
  - **S**tones (cholelithiasis)

- "Determine"
  - **D**isease
  - **E**ating poorly
  - **T**ooth loss
  - **E**conomic hardship
  - **R**educed social contact
  - **M**ultiple medications
  - **I**nvoluntary weight loss/gain
  - **N**eeds self-care assistance
  - **E**lder above age 80

Decreased Nutrient Bioavailability

Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements

Factors in Aging that Effect the Bioavailability of Nutrients[1]

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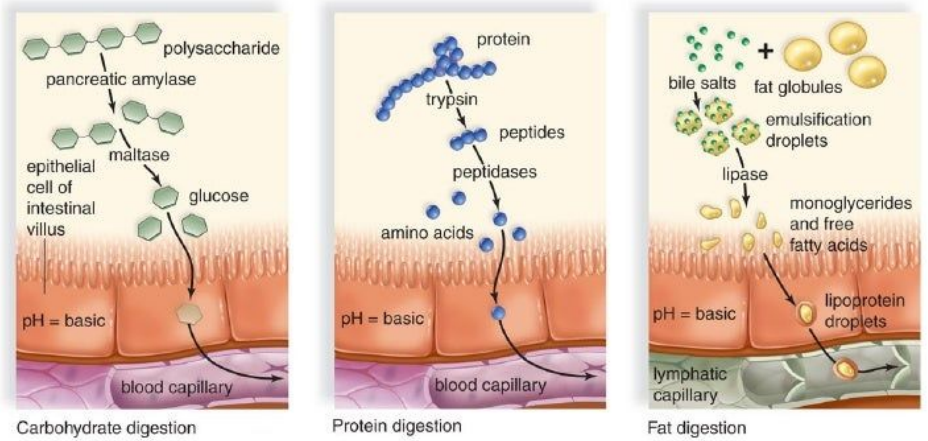
ABSTRACT Until a few years ago, little was known about bioavailability of micronutrients in elderly humans. It was assumed by many basic investigators and geriatricians that malabsorption of both macronutrients and micronutrients was a common problem among elderly persons. We now know that this is not the case; elderly persons who malabsorb macronutrients do so because of disease, not because of age. This report will be divided into three sections. The first section focuses on the general principles of absorptive processes in elderly persons. The second section focuses on the bioavailability of specific micronutrients in elderly persons, with specific examples of "problem" nutrients. The third section lays out a proposed research agenda for studying the bioavailability of nutrients and other active components of dietary supplements in elderly persons. J. Nutr. 131: 1359S–1361S, 2001.

Because of a large reserve capacity of both the pancreas and small intestine, elderly persons do not maldigest or malabsorb macronutrients. It has been shown that slight declines in both pancreatic secretion and small intestine absorptive capacity occur after repeated stimulation of the pancreas or by studying short segments of small intestine. When taking into account the total pancreatic reserve capacity and total small intestinal length, however, these small decreases in digestive and absorptive ability become clinically irrelevant. This was shown in a study (which is unlikely to ever be repeated) in ~100 elderly individuals who were placed on a 100-g fat diet while in a metabolic unit for a 6-d period (Arora et al. 1989). During the last 3 d, stools were collected, and fecal fat was measured. It was found that between the age range of ~20–95 y, there was no increase in fecal fat excretion due to age, thus disproving the commonly held notion of the time that malabsorption is common in elderly persons. As mentioned, if the system is stressed (e.g., through the intake of an extremely high fat diet of >120 g/d), elderly persons begin to show increases in fecal fat, whereas younger persons do not (Hambraeus 1972). Nevertheless, because such diets are unphysiologic, such a demonstration is not clinically pertinent.

A second principle to keep in mind when studying the bioavailability of nutrients in elderly persons is declining renal function with advancing age. This has been demonstrated in both men and women (Lindeman 1993, Sokoll et al. 1994). Renal function becomes a relevant issue to bioavailability when urinary excretion of a nutrient or nutrient metabolite is taken as a proxy measure of absorption and if the excretion of the specific nutrient or nutrient metabolite occurs primarily via by the kidney. The same holds true if the blood level of a nutrient or nutrient metabolite is influenced by renal function. An example of such a nutrient is dxylose: urinary D-xylose excretion after a 25-g oral load decreases with advancing age. However, when creatinine clearances are measured, the decline in the urinary D-xylose excretion due to age can be accounted for entirely by the decline in renal clearance, rather than by an intestinal absorptive defect (Arora et al. 1989). Similarly, measurement of vitamin B-12 bioavailability by Schilling tests or measurement of folate bioavailability by urinary excretion tests (as is done in the classic folic acid absorption test) in elderly individuals with declining kidney function might give the false impression of poor absorption, when in fact the intestinal absorption of these nutrients could be normal. Also, the metabolite homocysteine in blood is used to reflect folate status. If folate is administered to an individual with impaired renal function to correct a high serum homocysteine concentration and the concentration remains elevated, this might give the false impression that folate bioavailability is impaired (Hermann et al. 1999). Homocysteine

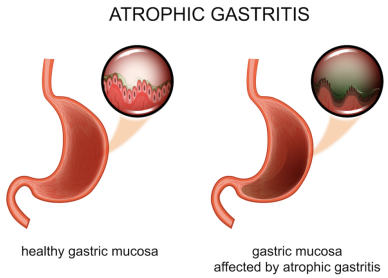
Decreased Nutrient Bioavailability

- Physiological roots
  - Decreases in small intestine absorption
  - Pancreatic enzyme secretion
  - Renal function
  - Slower uptake of fat-soluble nutrients from chylomicrons



Decreased Nutrient Bioavailability

- *Primarily driven by age-related disease… not age itself*
  - Atrophic gastritis
    - Approximately 20% older adults
    - Low stomach acid & pepsin -> low B12, folate, iron, calcium, carotenoids, etc.
    - Amino acids… sarcopenia



  - Other age-related diseases increase nutrient demands
    - Diabetes, cognitive decline, cancer, sarcopenia, etc.

Medication-related Nutrient Depletion

Table 1

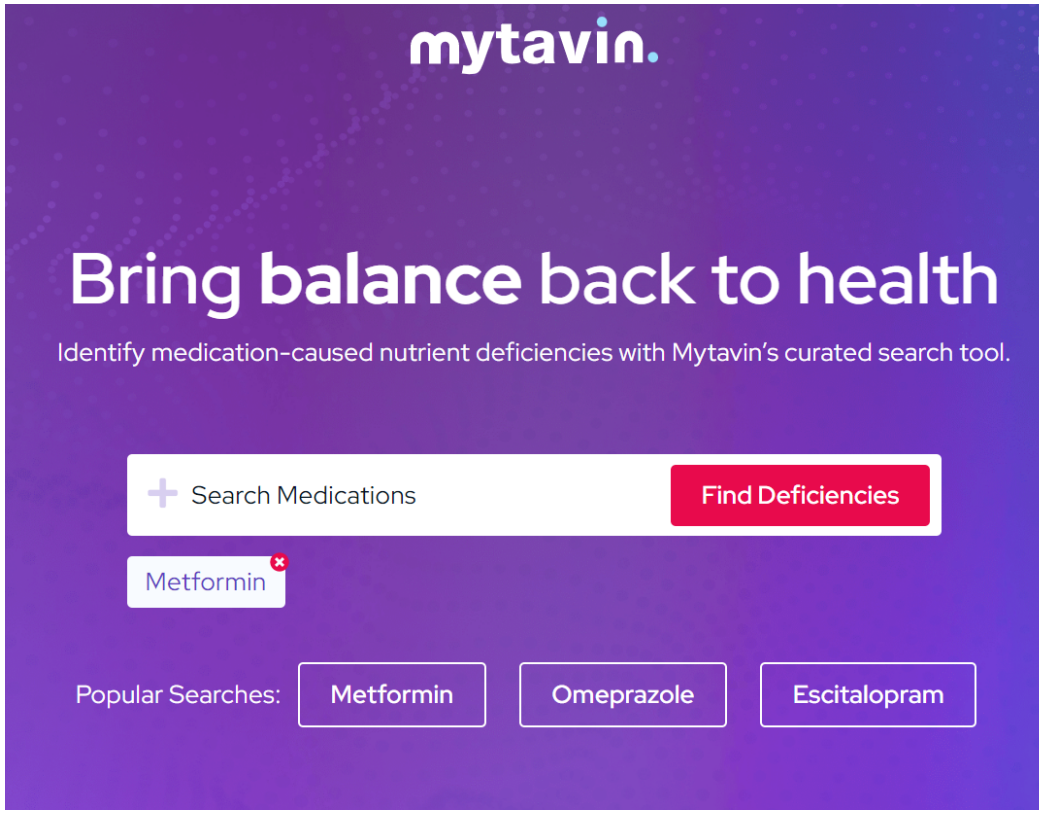
Common Drug-Nutrient Depletions

Nutrient Depletion	Causative Medications
Calcium	Anticonvulsants (e.g., phenytoin, carbamazepine) Corticosteroids H_2RAs Loop diuretics
Coenzyme Q10	Hydralazine
Folic acid	Anticonvulsants (e.g., phenytoin, carbamazepine) Estrogens (oral contraceptives) Pancreatic enzymes
Magnesium	Estrogens (oral contraceptives) H_2RAs Loop diuretics PPIs Thiazide diuretics
Potassium	Corticosteroids Loop diuretics Thiazide diuretics
Thiamine	Loop diuretics Thiazide diuretics
Vitamin A	Bile acid sequestrants
Vitamin B_{12}	Metformin H_2RAs PPIs
Vitamin D	Anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine) Bile acid sequestrants H_2RAs
Vitamin K	Bile acid sequestrants
Zinc	H_2RAs Loop diuretics Thiazide diuretics

H_2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor.
Source: References 4, 6, 10.

Mospan (2019) *US Pharm.* 44(12):18-24.

Medication-related Nutrient Depletion



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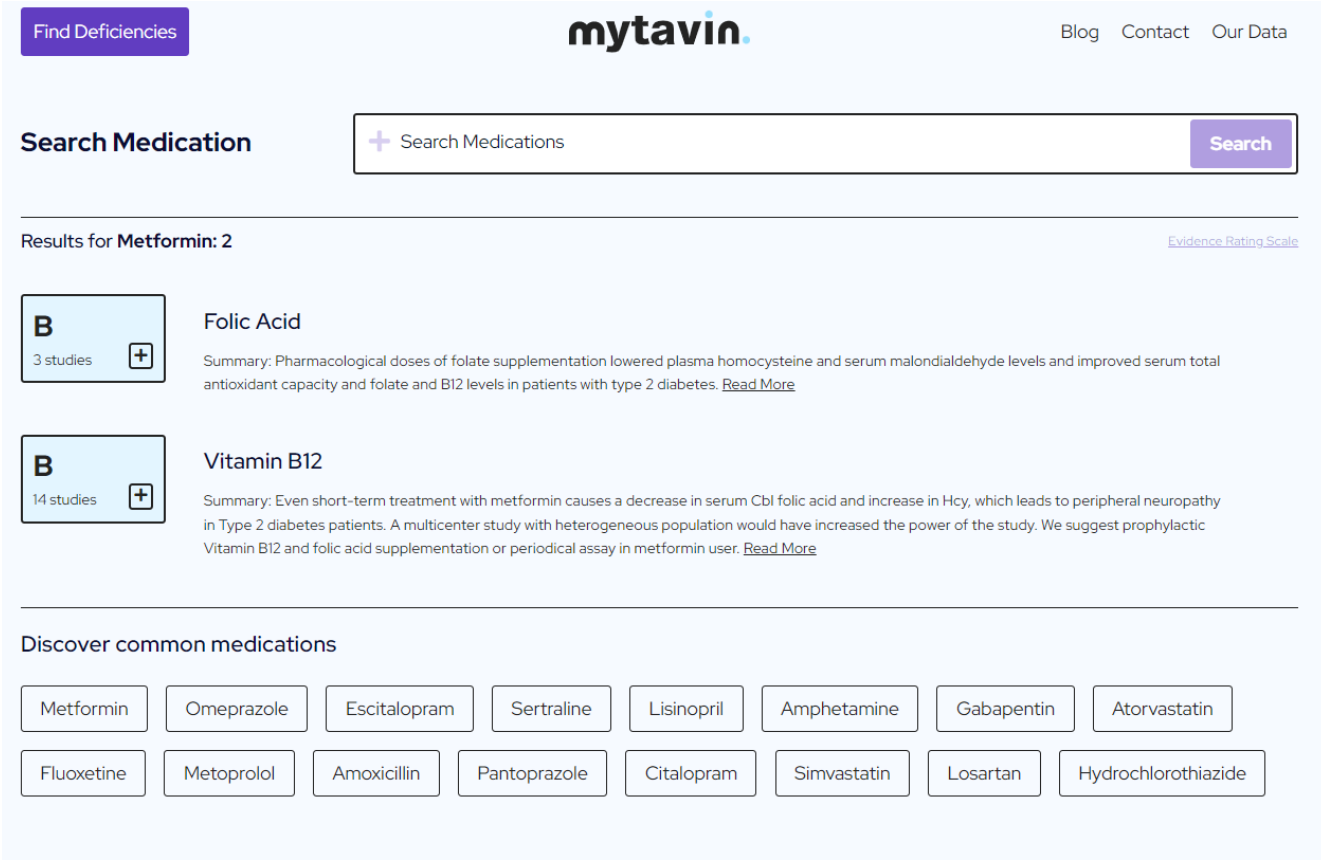
Medication-related Nutrient Depletion



Medication-related Nutrient Depletion

B
14 studies

Vitamin B12

B 2016

Even short-term treatment with metformin causes a decrease in serum Cbl folic acid and increase in Hcy, which leads to peripheral neuropathy in Type 2 diabetes patients. A multicenter study with heterogeneous population would have increased the power of the study. We suggest prophylactic Vitamin B12 and folic acid supplementation or periodical assay in metformin user.

B 2011

Pharmacological doses of folate supplementation lowered plasma homocysteine and serum malondialdehyde levels and improved serum total antioxidant capacity and folate and B12 levels in patients with type 2 diabetes.

B 2010

Long term treatment with metformin increases the risk of vitamin B-12 deficiency, which results in raised homocysteine concentrations. Vitamin B-12 deficiency is preventable; therefore, our findings suggest that regular measurement of vitamin B-12 concentrations during long term metformin treatment should be strongly considered.

D 2004

Even though the direct effect of metformin treatment on the plasma Hcy could not be concluded from the present study, it was found that there was a significant depletion of level of serum vitamin B12 among patients who had been on long-term metformin treatment. Therefore, vitamin B12 supplement is suggested for diabetic patients who are receiving metformin medication.

Medication-related Nutrient Depletion

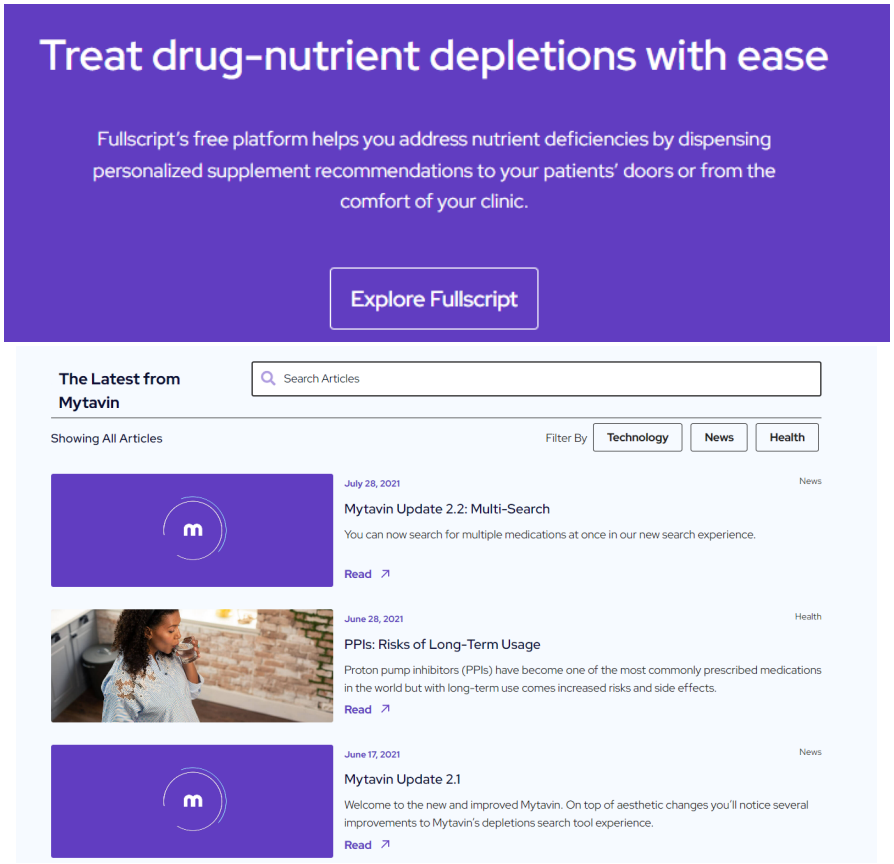
Level	Qualifying studies
A	Systematic review or meta-analysis of human trials
B	Human RDBPC trials. ≥ 2 studies and/or 1 study with ≥ 50 subjects
C	Human RDBPC trials or RCTs. 1 study < 50 subjects
D	Human trials or in-vivo animal trials
N/A	Insufficient evidence to suggest that any significant nutrient depletions exist

Our Data

The Mytavin Medical Review Board (MRB), which consists of licensed medical professionals, conducted a thorough search of the top prescribed pharmaceutical medications within reputable drug databases as well as peer-reviewed literature, including:

- PubMed
- U.S. Food & Drug Administration
- American Academy of Family Physicians
- Journal of the American Medical Association
- Science Direct
- Natural Medicines Database (TRC)

Medication-related Nutrient Depletion



Mechanism… Triage-Theory

PNAS PNAS PNAS PNAS

Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage

Bruce N. Ames*

Nutrition and Metabolism Center, Children's Hospital of Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA 94609

Contributed by Bruce N. Ames, October 6, 2006 (sent for review September 20, 2006)

Inadequate dietary intakes of vitamins and minerals are widespread, most likely due to excessive consumption of energy-rich, micronutrient-poor, refined food. Inadequate intakes may result in chronic metabolic disruption, including mitochondrial decay. Deficiencies in many micronutrients cause DNA damage, such as chromosome breaks, in cultured human cells or *in vivo*. Some of these deficiencies also cause mitochondrial decay with oxidant leakage and cellular aging and are associated with late onset diseases such as cancer. I propose DNA damage and late onset disease are consequences of a triage allocation response to micronutrient scarcity. Episodic shortages of micronutrients were common during evolution. Natural selection favors short-term survival at the expense of long-term health. I hypothesize that short-term survival was achieved by allocating scarce micronutrients by triage, in part through an adjustment of the binding affinity of proteins for required micronutrients. If this hypothesis is correct, micronutrient deficiencies that trigger the triage response would accelerate cancer, aging, and neural decay but would leave critical metabolic functions, such as ATP production, intact. Evidence that micronutrient malnutrition increases late onset diseases, such as cancer, is discussed. A multivitamin-mineral supplement is one low-cost way to ensure intake of the Recommended Dietary Allowance of micronutrients throughout life.

Poor nutrition has been linked to an increased risk of many diseases, including cancer, heart disease, and diabetes. The human diet requires both macronutrients, which are the main source of calories, and micronutrients (≈40 essential minerals, vitamins, and other biochemicals), which are required for virtually all metabolic and developmental processes. The leading dietary sources of energy in the United States are abundant in carbohydrates and fats (1) but deficient in micronutrients (i.e., they are energy-dense and nutrient-poor) (2). Such foods are inexpensive and tasty and as a conse-

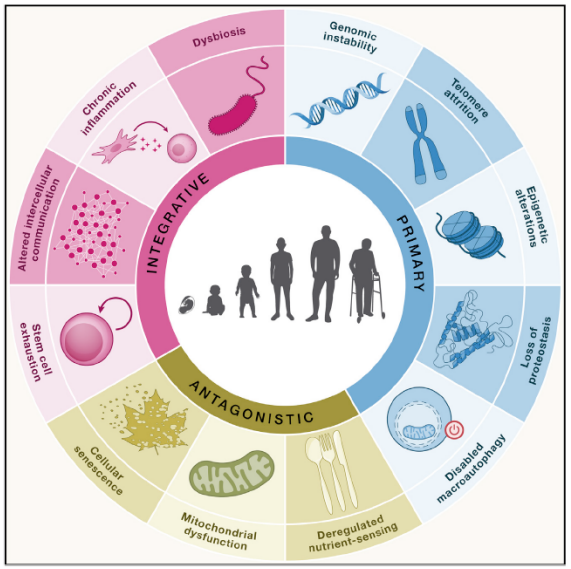
Table 1. Selected micronutrient inadequacy in the U.S.

Nutrient	Population group	% ingesting less than the EAR from food
Minerals		
Iron	Women 14–50 years old	16
Magnesium	All	56
Zinc	All	12
Vitamins		
B6	Women >71 years old	49
Folate	Adult women	16
E	All	93
C	All	31

Less than the EAR is used as a measure of inadequacy in populations (4, 5). The RDA is defined as 2 standard deviations above the EAR. Data are from Moshfegh *et al.* (4).

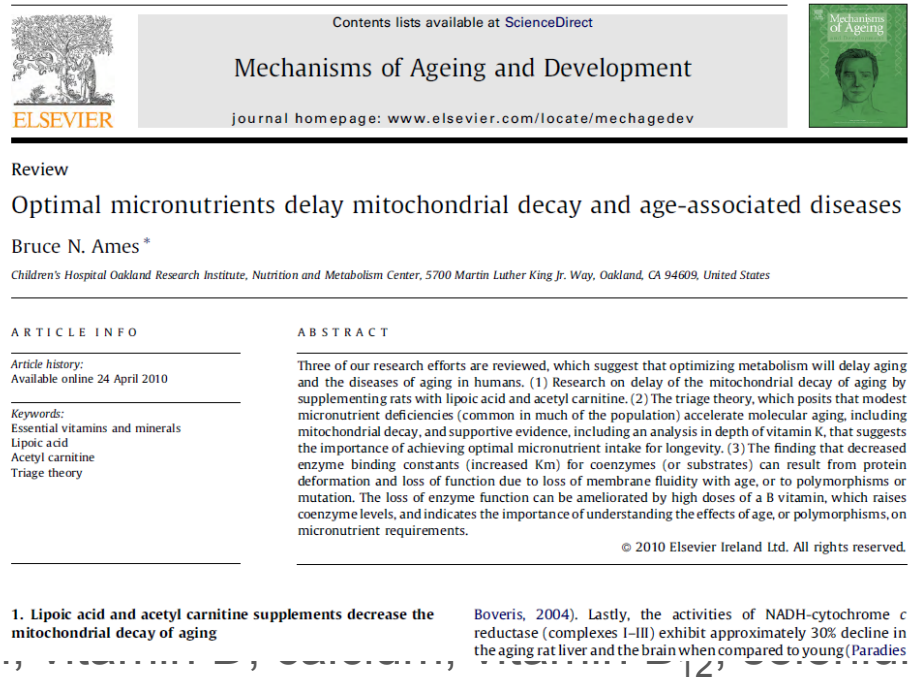
Mechanism… Triage-Theory

- Scarce nutrients triaged for “survival” at expense of…
  - Mitochondrial function, DNA repair, telomeres, senescence
    - Hallmarks of aging
    - Contributes to age-related disease



Mechanism… Triage-Theory

- Carnitine & alpha-lipoic acid of primary concern



Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Review

Optimal micronutrients delay mitochondrial decay and age-associated diseases

Bruce N. Ames *

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ARTICLE INFO

Article history:
Available online 24 April 2010

Keywords:
Essential vitamins and minerals
Lipoic acid
Acetyl carnitine
Triage theory

ABSTRACT

Three of our research efforts are reviewed, which suggest that optimizing metabolism will delay aging and the diseases of aging in humans. (1) Research on delay of the mitochondrial decay of aging by supplementing rats with lipoic acid and acetyl carnitine. (2) The triage theory, which posits that modest micronutrient deficiencies (common in much of the population) accelerate molecular aging, including mitochondrial decay, and supportive evidence, including an analysis in depth of vitamin K, that suggests the importance of achieving optimal micronutrient intake for longevity. (3) The finding that decreased enzyme binding constants (increased Km) for coenzymes (or substrates) can result from protein deformation and loss of function due to loss of membrane fluidity with age, or to polymorphisms or mutation. The loss of enzyme function can be ameliorated by high doses of a B vitamin, which raises coenzyme levels, and indicates the importance of understanding the effects of age, or polymorphisms, on micronutrient requirements.

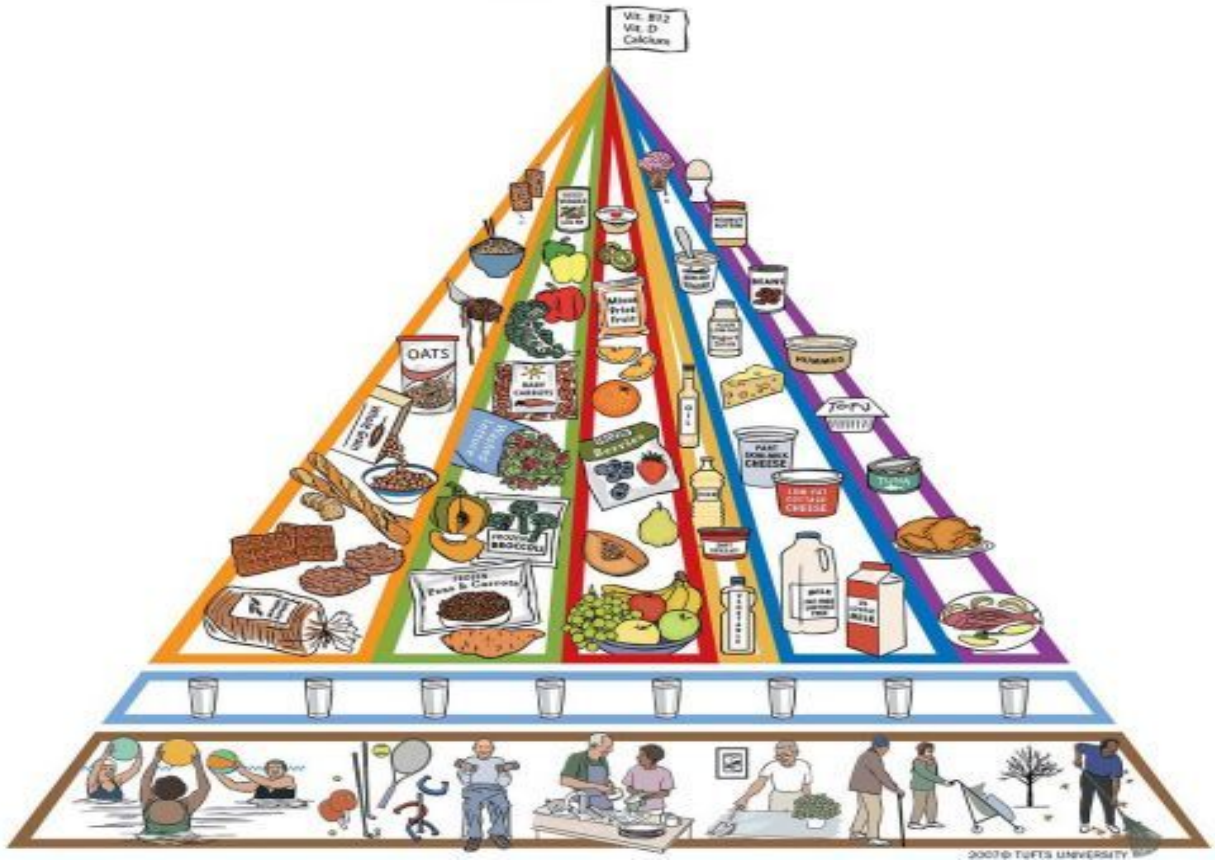
1. Lipoic acid and acetyl carnitine supplements decrease the mitochondrial decay of aging

Boveris, 2004). Lastly, the activities of NADH-cytochrome *c* reductase (complexes I–III) exhibit approximately 30% decline in the aging rat liver and the brain when compared to young (Paradies

- Others… magnesium, vitamin D, calcium, vitamin B_{12}, selenium…, iron, omega-3 fats
  - *Cover bases with high-quality multivitamin*

Strategies to address increased nutrient demands with aging

Tufts Food Pyramid For Older Adults



Unique Nutritional Needs with Aging

- Increased fluid intake
- Increased protein intake
- Increased intake of key micronutrients
  - Vitamin B_{12}
  - Calcium
  - Vitamin D
- Many other important nutritional factors for optimal aging & healthspan
  - Minerals: magnesium, zinc, etc.
  - Vitamins: B_1, B_3, C, E, K, folate, etc.
  - Non-essential nutrients: creatine, carotenoids, NAD+ precursors, etc.
  - Inflammation, protein bioavailability, nutrient timing, etc.

Hallmarks of Aging: Impact of Nutrition

PRIMARY

- Genomic instability
  - *Imbalance of DNA damage & repair*
  - Antioxidants, NrF2 activators (e.g. sulforaphane, curcumin, naringenin), sirtuin activators (e.g. NAD+ precursors, fucoidan, fasting), α-ketoglutarate
- Telomere attrition
  - *DNA damage at end of chromosomes*
  - Mediterranean diets, fiber, polyphenols (e.g. coffee), vitamin D, omega-3 fats
- Epigenetic alterations
  - *Deleterious changes in gene expression*
  - Methyl donors (e.g. SAM-e, TMG, choline, B vitamins, omega-3 fats), HDAC inhibitors (e.g. sulforaphane, EGCG, quercetin), α-ketoglutarate

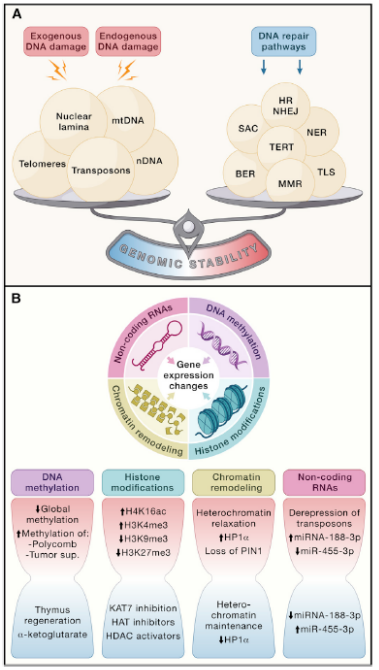
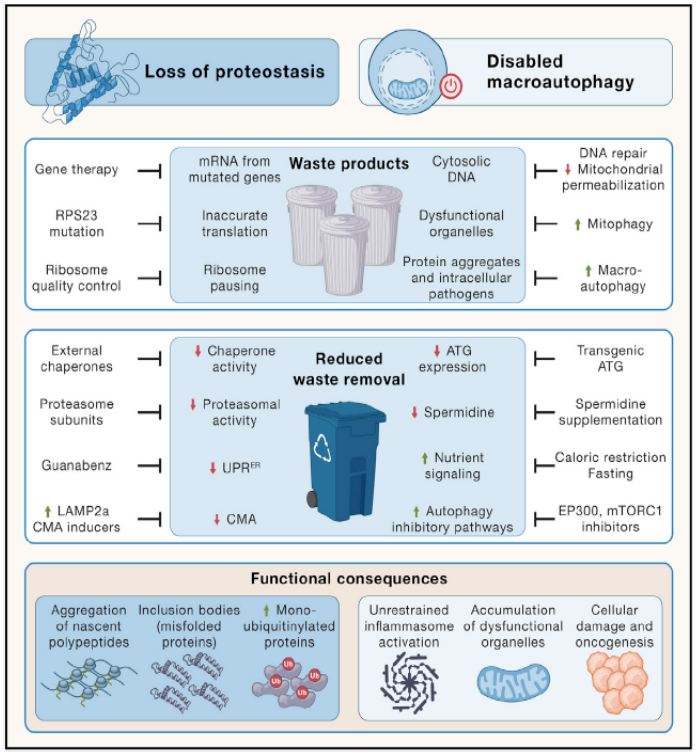


Figure 2. Loss of cellular integrity caused by genomic instability, telomere attrition, and epigenetic alterations

Hallmarks of Aging: Impact of Nutrition

PRIMARY

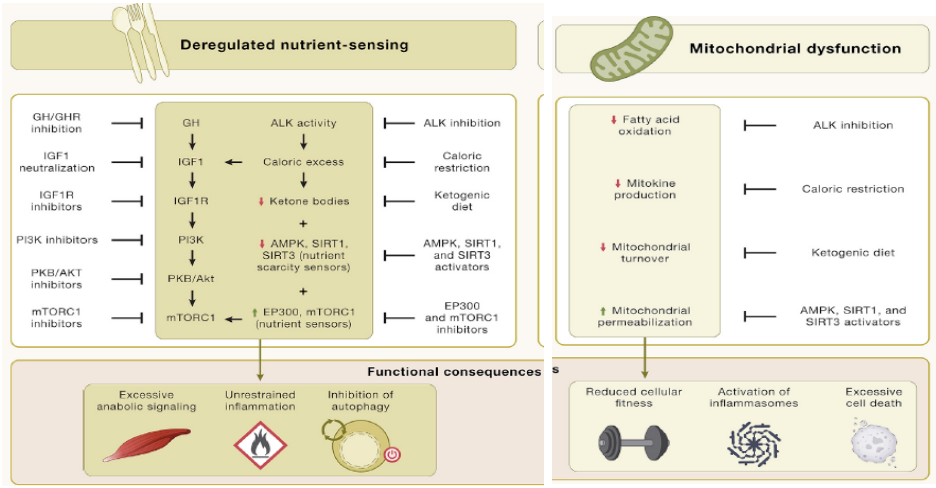
- Loss of proteostasis
  - *Misfolded, oxidized, glycated proteins*
  - Berberine, sulforaphane, spices/herbs, low temperature cooking
- Disabled macroautophagy
  - *Compromised waste removal*
  - Fasting, caloric restriction, urolithin A, spermidine, NAD+ precursors



Hallmarks of Aging: Impact of Nutrition

ANTAGONISTIC

- Deregulated nutrient sensing
  - *Altered anabolism, autophagy, inflammation*
  - Caloric restriction/fasting/time-restricted eating, ketogenic diet, berberine, adequate nutrients & no caloric excess
- Mitochondrial dysfunction
  - *Poor cellular function, inflammation*
  - L-carnitine, CoQ10, PQQ, ketogenic diet



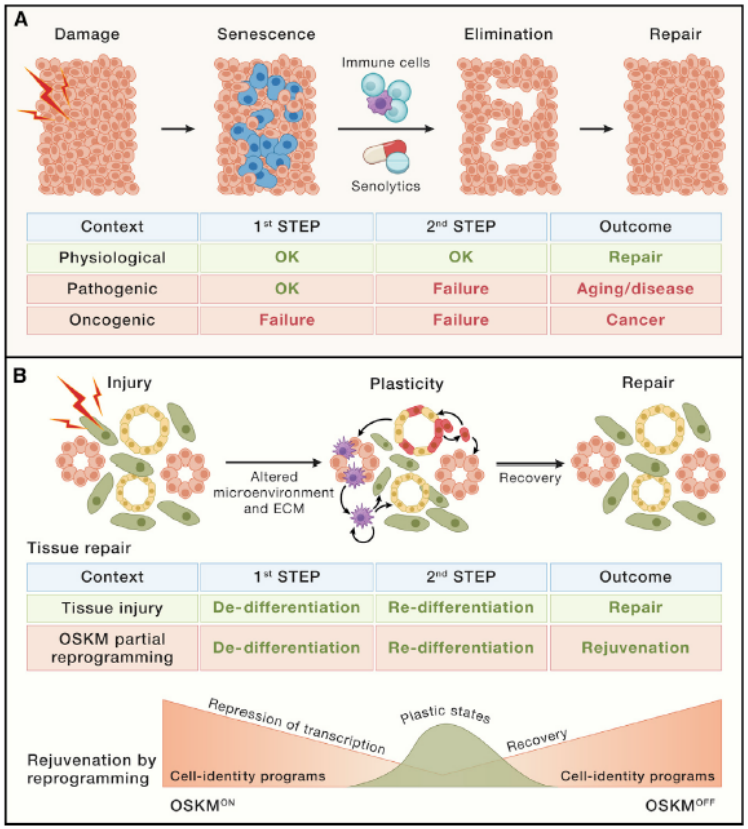
Hallmarks of Aging: Impact of Nutrition

ANTAGONISTIC

- Cellular senescence
  - *Inability to clear "zombie cells"*
  - Fisetin, quercetin, CR/fasting/time-restricted eating

INTEGRATIVE

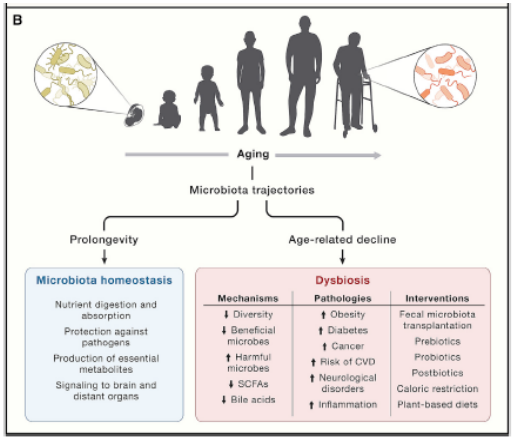
- Stem cell exhaustion
  - *Loss of cellular plasticity*
  - CR/fasting/time-restricted eating, ketogenic diet

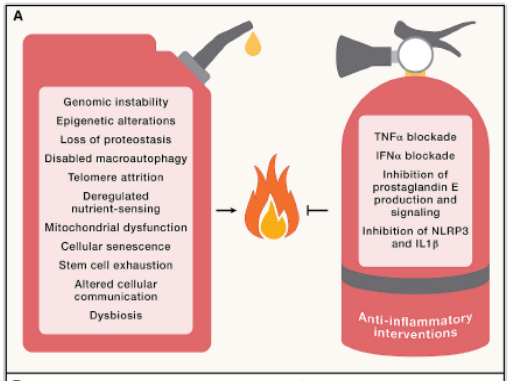


Hallmarks of Aging: Impact of Nutrition

INTEGRATIVE

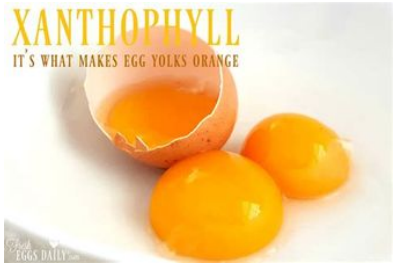
- Altered intercellular communication
  - *Deficiencies in signaling pathways*
  - Alpha lipoic acid, collagen/glucosamine&chondroitin/hyaluronic acid
- Dysbiosis
  - *↓ diversity, ↑ pathogens in gut microbiota*
  - Fermented foods, probiotics, prebiotics, SCFAs
- Chronic inflammation
  - *Consequence of other hallmarks*
  - Omega-3 fats, curcumin, polyphenols, EGCG, spices & herbs





"The question arises to which extent strategies for extending human healthspan should be based on the ***avoidance of age-accelerating environmental factors*** (such as pollution, stress, inadequate physical activity, and unhealthy diets, often unavoidable in a context of poverty, precariousness, and wartime), **the adoption of health-promoting lifestyle factors** (such as ***diet***, exercise, regular sleeping patterns, and social activities), the **administration of relatively non-specific, pleiotropic drugs** (exemplified by NAD+ precursors, metformin, spermidine, or MTORC1 inhibitors), or more specific medical interventions."

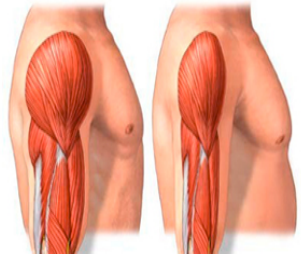
Lopez-Otin et al. (2023) *Cell* 186(2):243-278.


XANTHOPHYLL
IT'S WHAT MAKES EGG YOLKS ORANGE

Protein

Protein Intake

- Decrease in total body protein with age
  - Clinical manifestation
    - Decreased skeletal muscle mass
  - Subclinical manifestation
    - Organ tissue, immune system, blood components



- Massive skeletal muscle decrease
  - Young adults – skeletal muscle 45% total body weight
  - Age 70 – skeletal muscle 27% total body weight
- Dietary protein builds and maintains skeletal muscle
  - Dietary protein → amino acids → builds skeletal muscle
- High-quality protein intake key to prevent sarcopenia

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: A systematic review and meta-analysis

Ping Liu[1], Qiukui Hao[1], Shan Hai, Hui Wang, Li Cao, Birong Dong*

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ARTICLE INFO

Keywords:
Sarcopenia
All-cause mortality
Meta-analysis

ABSTRACT

The aim of this systematic review and meta-analysis was to examine the association between sarcopenia and all-cause mortality among community-dwelling older people.

A systematic review was performed using three electronic databases (EMBASE, MEDLINE and the Cochrane Library) to identify prospective cohort studies from January 2009 to February 2017 examining sarcopenia as a predictor of all-cause mortality among community–dwelling older people. We conducted a pooled analysis of mortality associated with sarcopenia, and subgroup analyses based on measurements of muscle mass and length of follow-up by employing a random-effects model. Sensitivity analyses were performed evaluate the cause of high heterogeneity. In addition, methodological quality, heterogeneity and publication bias were evaluated.

Of 1703 studies identified, 6 studies incorporating 7367 individuals were included in the meta-analysis for all-cause mortality. The pooled hazard ratios (HRs) of all-cause mortality from the combination of included studies suggested participants with sarcopenia had a significantly higher rate of mortality (pooled HR 1.60, 95%CI 1.24–2.06, I^2 = 27.8%, p = 0.216) than participants without sarcopenia. The subgroup analysis for length of follow-up suggested studies with a follow-up period of less than 5 years found a higher risk of all-cause mortality (pooled HR 2.09, 95%CI 1.21–3.60) than studies with a follow-up period of 5 years or more (pooled HR 1.52, 95%CI 1.14–2.01). A subgroup of anthropometric measures was found to identify higher mortality risks (pooled HR 2.26, 95%CI 1.30–3.92) than a subgroup of dual-energy x-ray (DXA) absorptiometry (pooled HR 1.82, 95%CI 1.04–3.18) factors or a subgroup of bioelectrical impedance analysis (BIA) factors (pooled HR 1.31, 95%CI 1.15–1.49).

Sarcopenia is a predictor of all-cause mortality among community-dwelling older people. Therefore, it is important to diagnose sarcopenia and to intervene, in order to reduce mortality rates in the elderly.

Protein Intake: Recommendations

- Older adults need more protein than RDA[1,2,3]
  - RDA for protein 0.8 g/kg body weight
    - RDA: 150 lb woman needs 54 grams protein per day
  - Research suggests *at least* 1 g/kg body weight
    - Research: Older 150 lb woman needs ≥ 68 grams protein per day
    - Some argue even more optimal for certain conditions
- Other repercussions of insufficient protein
  - Weakness and disability, impairments in immune function, wound & fracture healing, skin problems
  - ≥ 1 g/kg body weight required for these conditions[2,3,4]
- No evidence of renal harm to healthy kidneys

1.) Gersovitz et al (1982) *American Journal of Clinical Nutrition*; 2.) Campbell et al (1996) *European Journal of Clinical Nutrition*; 3.) Milward et al (1997) *American Journal of Clinical Nutrition*; 4.) Kurpad (2000) *European Journal of Clinical Nutrition*

Protein Intake: Quality

Protein quality assessment: impact of expanding understanding of protein and amino acid needs for optimal health[1–4]

D Joe Millward, Donald K Layman, Daniel Tomé, and Gertjan Schaafsma

ABSTRACT

Protein quality describes characteristics of a protein in relation to its ability to achieve defined metabolic actions. Traditionally, this has been discussed solely in the context of a protein's ability to provide specific patterns of amino acids to satisfy the demands for synthesis of protein as measured by animal growth or, in humans, nitrogen balance. As understanding of protein's actions expands beyond its role in maintaining body protein mass, the concept of protein quality must expand to incorporate these newly emerging actions of protein into the protein quality concept. New research reveals increasingly complex roles for protein and amino acids in regulation of body composition and bone health, gastrointestinal function and bacterial flora, glucose homeostasis, cell signaling, and satiety. The evidence available to date suggests that quality is important not only at the minimum Recommended Dietary Allowance level but also at higher intakes. Currently accepted methods for measuring protein quality do not consider the diverse roles of indispensable amino acids beyond the first limiting amino acid for growth or nitrogen balance. As research continues to evolve in assessing protein's role in optimal health at higher intakes, there is also need to continue to explore implications for protein quality assessment. *Am J Clin Nutr* 2008;87(suppl):1576S–81S.

INTRODUCTION

As addressed in earlier papers in this supplement and at the Summit, there is strong evidence emerging of a positive role for protein in promoting optimal health at intakes beyond the Recommended Dietary Allowance. There is new focus on the roles this has been discussed solely in the context of a food protein's ability to provide specific patterns of amino acids to satisfy the demands for synthesis of protein and other specific metabolites. As understanding of protein's actions expands beyond its role in maintaining body protein mass and satisfying metabolic demands for biosynthetic pathways, it is clear that the concept of protein quality must expand to incorporate these newly emerging actions of protein.

Which protein characteristics are important for which processes or functions? In the context of a brief review of the strengths and weaknesses of current methods for assessing protein quality, this paper will explore particular characteristics of the protein consumed that could impact optimal health and would need to be considered in an expanded protein quality concept. Clearly, for this newly emerging area, our main objective will be to define research questions for future exploration.

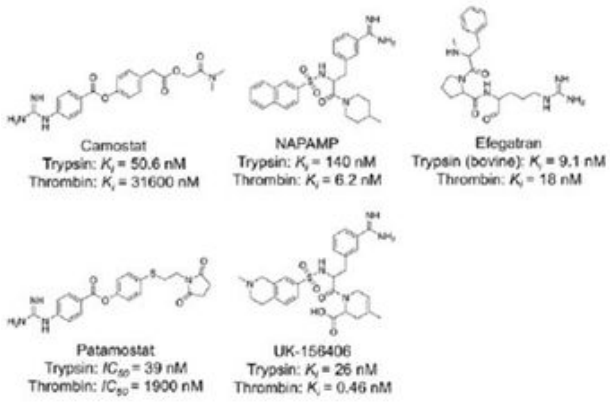
DEFINING PROTEIN QUALITY

It is a long-accepted paradigm that protein quality is an important aspect of any consideration of human protein needs, as evidenced by extensive efforts to measure quality and standardize those measurements. For this reason, in the present context of optimal protein intakes, discussion of "what sort" is equally relevant as the question of "how much."

There are 2 important aspects of protein quality: *1*) the characteristics of the protein and the food matrix in which it is consumed, and *2*) the demands of the individual consuming the food, as influenced by age, health status, physiologic status, and energy balance. Multiple factors influence protein quality, and these

Protein Intake: Quality

- Many dimensions of protein quality
  - *Classic* - Maintain body protein mass
  - Amino acid content
  - Body composition
  - Bone health
  - GI function
  - Cell signaling
  - Glucose homeostasis
  - Satiety
  - Accompanying nutrients & anti-nutrients (lectins, trypsin inhibitors)



- Not all proteins created equally… ***THINK QUANTITY AND QUALITY***

Protein Intake: Quality

British Journal of Nutrition

Advantages and limitations of the protein digestibility-corrected amino acid score (PDCAAS) as a method for evaluating protein quality in human diets

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(Submitted 27 July 2011 – Final revision received 1 November 2011 – Accepted 13 December 2011)

Abstract

PDCAAS is a widely used assay for evaluating protein quality. It is a chemical score, which is derived from the ratio between the first limiting amino acid in a test protein and the corresponding amino acid in a reference amino acid pattern and corrected for true faecal N digestibility. Chemical scores exceeding 100% are truncated to 100%. The advantages of the PDCAAS are its simplicity and direct relationship to human protein requirements. The limitations are as follows: the reference pattern is based on the minimum amino acid requirements for tissue growth and maintenance and does not necessarily reflect the optimum intake. Truncated PDCAAS of high-quality proteins do not give any information about the power of these proteins to compensate, as a supplement, for low levels of dietary essential amino acids in low-quality proteins. It is likely that faecal N digestibility does not take into account the loss from the colon of indispensable amino acids that were not absorbed in the ileum. Anti-nutritional factors, such as lectins and trypsin inhibitors, in several plant protein sources can cause heightened endogenous losses of amino acids, an issue which is particularly relevant in animal feedstuffs. The assumption that amino acid supplementation can completely restore biological efficiency of the protein source is incorrect since the kinetics of digestion and absorption between supplemented free amino acids and amino acids present in dietary proteins, are different.

Key words: Protein quality: PDCAAS: Advantages: Limitations: Improvements

Dietary proteins differ in their capacity to satisfy the metabolic demand for the nine dietary indispensable amino acids and nitrogen. Digestibility and the extent to which the absorbed amino acid pattern matches that of the requirement pattern are critical for the nutritional quality of single proteins and protein mixtures. In the past, protein quality was measured merely in growth experiments with rats and expressed in parameters like PER (Protein Efficiency Ratio) and NPU (Net Protein Utilization). The PER compares the growth response of young rats, fed a marginal amount of a test protein, with that of control multiplying this amino acid score by true faecal N digestibility (%), as measured in a rat assay.

$$\text{PDCAAS (\%)} = \text{amino acid score (AAS)} \times \text{true N digestibility (TD) (\%)}$$

$$\text{AAS} = \text{Content of first limiting amino acid in a test protein (mg/g)} \Big/ \text{Content of corresponding amino acid in a reference protein (mg/g)}$$

Protein Intake: Bioavailability

- Bioavailability
  - Animal proteins > plant proteins

Protein Source	Bio Availability Index
Whey Protein Isolate Blends	100-159
Whey Concentrate	104
Whole Egg	100
Cow's Milk	91
Egg White	88
Fish	83
Beef	80
Chicken	79
Casein	77
Rice	74
Soy	59
Wheat	54
Beans	49
Peanuts	43

Protein Intake: Amino Acids

- Leucine particularly important for muscle maintenance

TABLE 1
Leucine and BCAA content of foods[1–3]

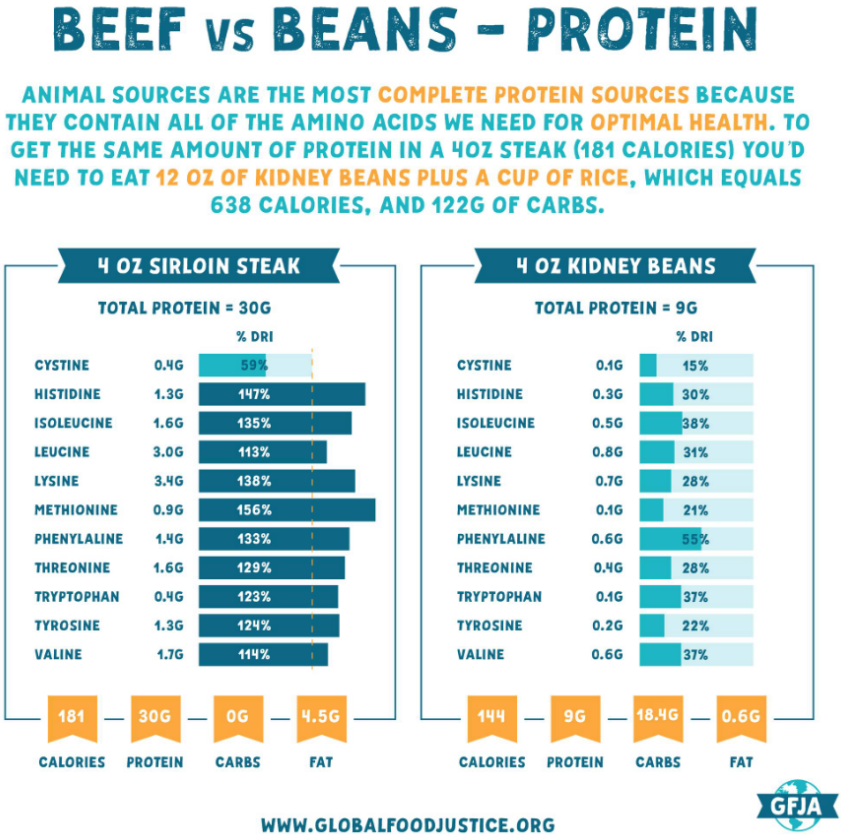
	Leucine	BCAA
Whey protein isolate	14%	26%
Milk protein	10%	21%
Egg protein	8.5%	20%
Muscle protein	8%	18%
Soy protein isolate	8%	18%
Wheat protein	7%	15%

[1] Values reflect g amino acids/100 g protein. BCAA, branched-chain amino acid.

[2] Adapted from Layman and Baum (12).

[3] Source: USDA Food Composition Tables.

Protein Intake: Amino Acids



Dietary Protein

- *Practical tips*
  - Ensure adequate leucine intake
  - Encourage animal protein intake
    - If uncomfortable with meat/fish/shellfish
      - Pasture-raised eggs & grass-fed dairy
      - Whey protein powder supplementation ideal
    - If vegan
      - Encourage consideration of amino acids… not just grams of protein
      - Many plant-based protein powders have amino acid content on label

Ingredients: Proprietary Protein Blend (Raw Organic Pea Protein, Raw Cranberry Protein, Raw Organic Hemp Seed Protein), Medium Chain Triglycerides

AMINO ACID PROFILE

Per Serving

Alanine	864 mg
Arginine	1783 mg
Aspartic Acid	2265 mg
Cystine	210 mg
Glutamic Acid	3470 mg
Glycine	854 mg
Histidine	501 mg
Isoleucine	864 mg
Leucine	1728 mg
Lysine	1793 mg
Methionine	198 mg
Phenylalanine	1095 mg
Proline	1148 mg
Serine	1076 mg
Threonine	596 mg
Tryptophan	160 mg
Tyrosine	761 mg
Valine	948 mg

Dietary Protein

- *Practical tips*
  - Avoid plant-based meat as primary protein source
    - Poor-quality protein

"Something is really wrong at Beyond Meat"; New Lawsuit Filed Against Beyond Meat and CEO Ethan Brown on behalf of Don Lee Farms

LOS ANGELES--(BUSINESS WIRE)--A new federal lawsuit was filed today against Beyond Meat and its CEO Ethan Brown alleging false advertising and unfair competition. The suit, filed in the Central District of California, claims that Beyond Meat overstates the protein value of its products by up to 30% and has falsely represented that its products are free from "synthetic" ingredients.

FULL INGREDIENT LIST:
WATER, TEXTURED WHEAT PROTEIN, COCONUT OIL, POTATO PROTEIN, NATURAL FLAVORS, 2% OR LESS OF: LEGHEMOGLOBIN (SOY), YEAST EXTRACT, SALT, KONJAC GUM, XANTHAN GUM, SOY PROTEIN ISOLATE, VITAMIN E, VITAMIN C, THIAMIN (VITAMIN B1), ZINC, NIACIN, VITAMIN B6, RIBOFLAVIN (VITAMIN B2), VITAMIN B12

REVIEW

doi:10.1038/nature11861

mTOR is a key modulator of ageing and age-related disease

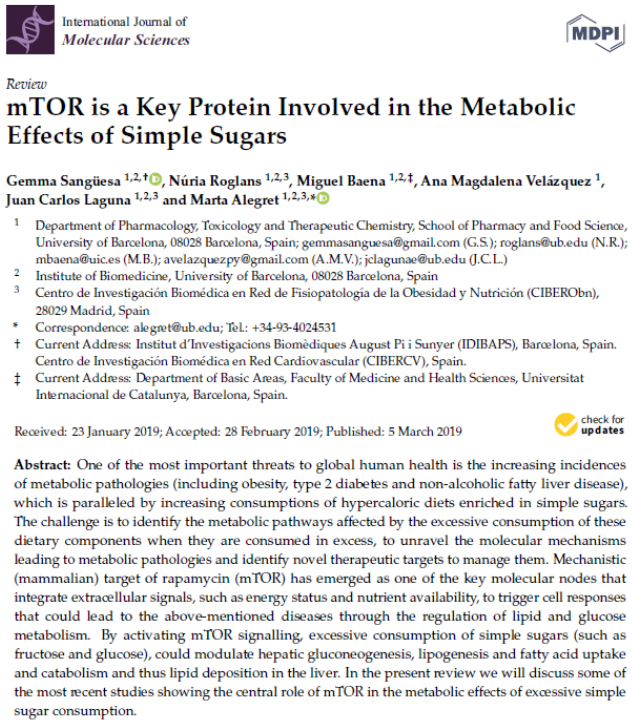
Simon C. Johnson[1], Peter S. Rabinovitch[1] & Matt Kaeberlein[1,2]

Many experts in the biology of ageing believe that pharmacological interventions to slow ageing are a matter of 'when' rather than 'if'. A leading target for such interventions is the nutrient response pathway defined by the mechanistic target of rapamycin (mTOR). Inhibition of this pathway extends lifespan in model organisms and confers protection against a growing list of age-related pathologies. Characterized inhibitors of this pathway are already clinically approved, and others are under development. Although adverse side effects currently preclude use in otherwise healthy individuals, drugs that target the mTOR pathway could one day become widely used to slow ageing and reduce age-related pathologies in humans.

Dietary Protein: mTOR

- Mechanistic target of rapamycin (mTOR)
  - Inhibition of pathway suppresses growth
  - Increased longevity in non-human species

- Cyclic mTOR inhibition likely beneficial
  - Could involve *occasional* protein restriction…
    - … but glucose also activates mTOR!
    - Sanguesa et al (2019) *Int J Mol Sci* 20(5):1117.



International Journal of *Molecular Sciences*

MDPI

Review

mTOR is a Key Protein Involved in the Metabolic Effects of Simple Sugars

Gemma Sangüesa [1,2,†], Núria Roglans [1,2,3], Miguel Baena [1,2,†], Ana Magdalena Velázquez [1], Juan Carlos Laguna [1,2,3] and Marta Alegret [1,2,3,*]

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check for updates

Abstract: One of the most important threats to global human health is the increasing incidences of metabolic pathologies (including obesity, type 2 diabetes and non-alcoholic fatty liver disease), which is paralleled by increasing consumptions of hypercaloric diets enriched in simple sugars. The challenge is to identify the metabolic pathways affected by the excessive consumption of these dietary components when they are consumed in excess, to unravel the molecular mechanisms leading to metabolic pathologies and identify novel therapeutic targets to manage them. Mechanistic (mammalian) target of rapamycin (mTOR) has emerged as one of the key molecular nodes that integrate extracellular signals, such as energy status and nutrient availability, to trigger cell responses that could lead to the above-mentioned diseases through the regulation of lipid and glucose metabolism. By activating mTOR signalling, excessive consumption of simple sugars (such as fructose and glucose), could modulate hepatic gluconeogenesis, lipogenesis and fatty acid uptake and catabolism and thus lipid deposition in the liver. In the present review we will discuss some of the most recent studies showing the central role of mTOR in the metabolic effects of excessive simple sugar consumption.

Dietary Protein: mTOR

- Fasting/time-restricted eating preferable strategy
  - Within reason in advanced age, e.g. “16/8”
  - Excessive time-restricted eating not recommended among older adults
- Potentially: cyclic rapamycin, metformin, berberine
  - Need more studies
- Need for protein > mTOR inhibition among older adults
  - Protein restriction not advised

More on mTOR

Fasting, Longevity, Autophagy & mTOR Inhibitors - Peter Attia, MD

High Intensity Health
608K subscribers

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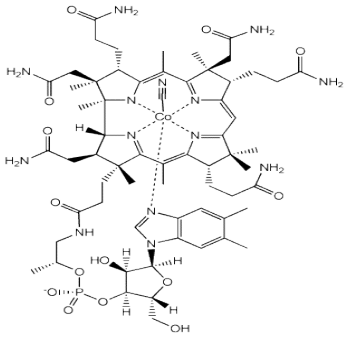
Vitamins, Minerals,
Essential Nutrients

Vitamin B_{12}

- Largest and most complex vitamin
  - Contains metal ion (cobalt)… called cobalamin
  - Essential physiological functions
    - Red blood cell formation, nerve cell generation, methylation
    - Metabolism of food (macronutrients) → ENERGY
- Protective against many diseases
  - CVD, neurological disease, Alzheimer's, depression, etc.
  - Deficiency common… older adults and especially vegans
    - Up to 60% of institutionalized older adults and 90% of vegans
    - Poor digestion contributes to deficiency among older adults
- Depleted by many common medications
  - Acid-blocking medications (Prilosec, Tagamet, etc.)
  - Anti-diabetic medications (Avandia, Metformin, etc.)



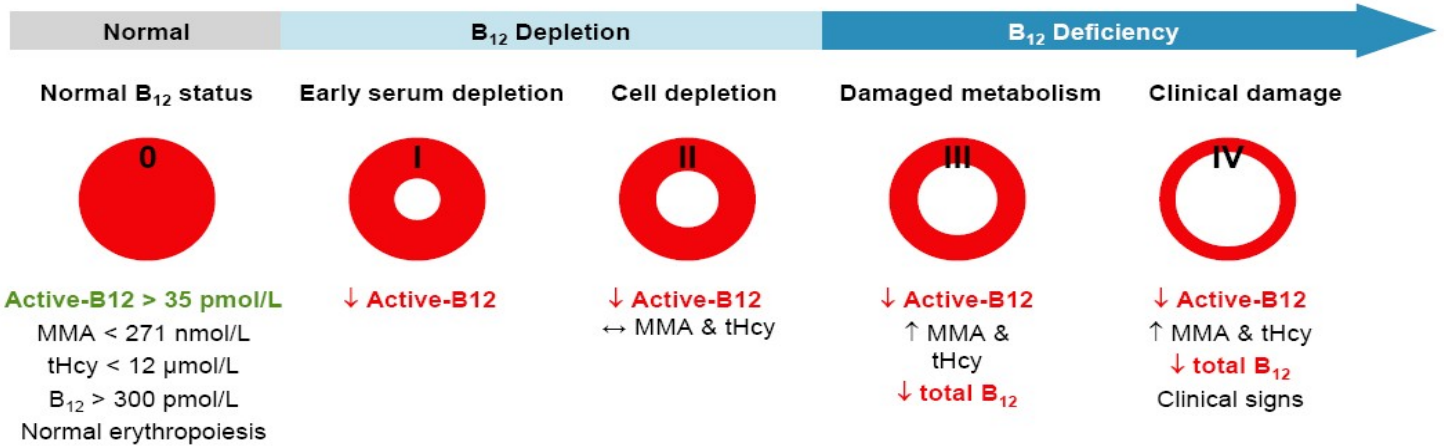
Vitamin B_{12}: Sources

- Dietary sources

- Consider supplement (methylcobalamin) when…
  - Low serum B_{12} and/or low MMA and/or high homocysteine
  - Vegetarian or vegan diet
  - Taking B_{12}-depleting medications
    - Acid-reducing medications, anti-diabetic medications
  - Consider *FUT2, FUT6, CD320, MTHFR, MTRR* SNPs

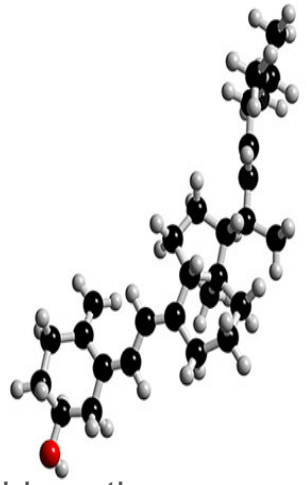
Vitamin B_{12}: Testing

- Serum B_{12}… plus methylmalonic acid (MMA), homocysteine, holotranscobalamin (holoTC)
  - Serum B_{12} does not reflect concentration in cells
  - 80% of serum B_{12} biologically unavailable to cells… available 20% attached to holotranscobalamin (holoTC)
  - Serum B_{12} assays underestimate deficiency!

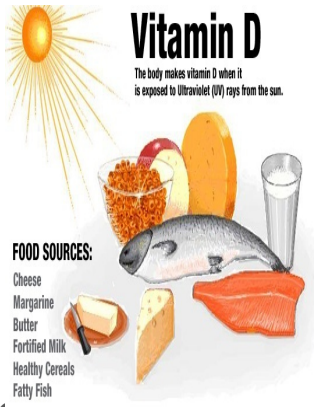


Vitamin D

- A uniquely important vitamin
  - Hormone (secosteroid)
  - Controls expression of hundreds of genes
    - Important role in many important human functions
- Vitamin D active in most biological systems
  - Musculoskeletal system
    - Classically emphasized role
    - *Necessary for calcium absorption*… calcium without vitamin D problematic
  - Endocrine system
  - Nervous system
  - Cardiovascular system
  - Digestive system
  - Immune system



Vitamin D: Sources

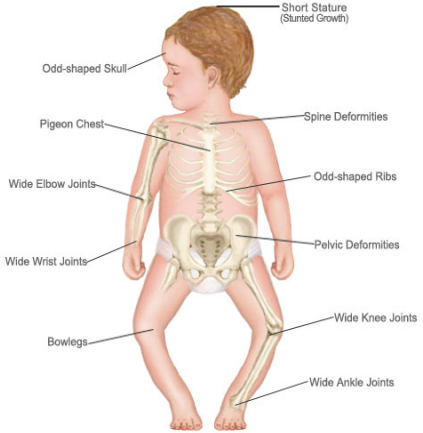


- Sun exposure
  - UVB light converted to vitamin D3 in skin
  - D3 transported to liver, metabolized to 25(OH)D
    - Also called calcidiol… measured most vitamin D blood tests
  - 25(OH)D converted to calcitriol in kidneys
  - ≈ 20,000 international units (IU) from 30 minutes sun exposure
    - Only spring and summer if north of Atlanta
- Limited amount from foods
  - D3 from oily fish, eggs, butter, cheese, fortified milk/cereals
    - Vitamin D is fat-soluble… needs fat for absorption
    - 10-100 IU: depending upon source
  - Supplements deliver much higher doses… up to 10,000 IU per pill
    - Acute vitamin D toxicity very rare... usually food fortification mistakes
      - Acute D3 toxicity intake ≈ 176,000,000 IU… 440,000 400 IU capsules
    - Chronic D3 toxicity even more rare

Vitamin D: RDA

- Current RDA varies
  - Age < 70 yrs: 600 IU
  - Age ≥ 70 yrs: 800 IU

- Amount to prevent vitamin D deficiency
  - Rickets
    - Softening of bones → deformities, fractures, etc.
    - Most common in children
    - Can also occur in older adults… called osteomalacia

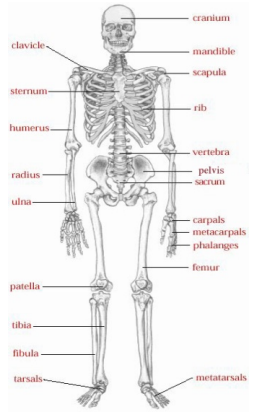


- Amount to prevent many chronic diseases likely higher
  - Call to substantially increase RDI to at least 1,000 IU
  - Explosion in vitamin D research
    - Bone disorders... immune health, cardiovascular health, cancer

Vitamin D: Recommendations

- Convincing evidence: 25(OH)D test
  - Vitamin D inadequacy extremely common
    - Between 36-100% depending on group, 2006 *Mayo Clinic Proceedings*
- Consider supplementation (vitamin D_3) when…
  - Advanced age
  - Low BMD/osteopenia/osteoporosis
  - Live north of Atlanta in fall & winter
    - Cannot synthesize from sun
  - Have darker skin tone
    - Less efficient synthesis in skin
  - Avoid sun or wear sunscreen
    - Most vitamin D from sun exposure
  - Low serum 25(OH)D
  - Consider *VDR* SNPs

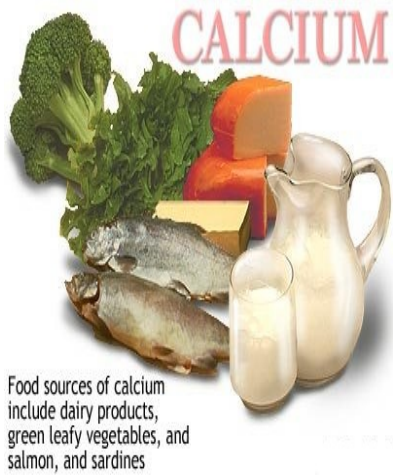
Calcium



- Mineral essential to healthy bone
  - 99% calcium stored in bone and teeth
  - Calcium and phosphorous form calcium phosphate
    - Major component of bone provides structure and strength
- Calcium other essential physiological functions
  - Blood clotting, muscle contraction, nerve conduction, regulation of enzyme activity, cell membrane function
  - *Helps eliminate oxalates*… Sally Norton work
- Regulation: low calcium in blood, extract from bone
  - Low Ca intake → low blood Ca → extract bone Ca → osteoporosis
- Calcium intake prevents and helps treat osteoporosis

Calcium: Sources

- Dietary sources



Food sources of calcium include dairy products, green leafy vegetables, and salmon, and sardines

- Consider supplement (*with vitamin D & K2*) when…
  - Postmenopausal women or low BMD/osteopenia/osteoporosis
  - Lactose intolerant or others who avoid dairy
  - Taking calcium-depleting medications
    - Acid-blocking medications, aluminum containing antacids, laxatives, certain antibiotics (aminoglycosides), digoxin (monitor blood levels)
  - Consider *GC* SNPs

Magnesium

- Mineral involved in > 300 physiological processes
  - 60% magnesium in bone… major role in bone health
    - Involved in calcium & vitamin D metabolism
  - Also important in protein synthesis, nerve & muscle function
- Magnesium intake protects against chronic disease
  - Osteoporosis, cardiovascular disease, hypertension, etc.
- Magnesium deficiency very common
  - Magnesium RDA not met at all ages… especially older adults
  - Older adults: 420 mg/day men, 320 mg/day women

Magnesium: Sources

- Dietary sources

World's Healthiest Foods rich in magnesium

Food	Cals	%Daily Value
Pumpkin Seeds	180	47.7%
Spinach	41	39.1%
Swiss Chard	35	37.6%
Soybeans	298	36.9%
Sesame Seeds	206	31.5%
Halibut	159	30.3%

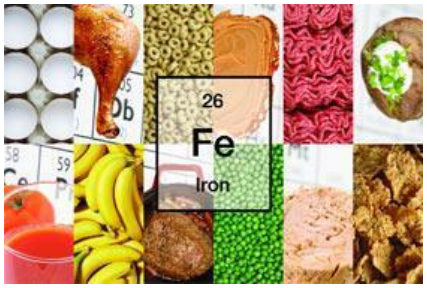
- Consider supplement (magnesium citrate, orotate, glycinate, chelate, etc… not magnesium oxide):
    - Not eating leafy green vegetables, seafood, bone broth
    - GI disorders, muscle problems, heart arrhythmia, etc.
    - Taking magnesium-depleting medications
        - Digoxin, diuretics (Lasix), likely others

Magnesium

- Serum does not reflect total body magnesium levels
  - Most common lab test
  - < 1% of total body magnesium in serum… most in bone & cells
  - Serum magnesium strictly regulated, extracted from cells when low… serum magnesium limited clinical meaning
  - Magnesium deficiency underestimated by serum alone
- *How to best test your magnesium levels?*
  - Red blood cell (RBC) magnesium
  - Magnesium tolerance test
    - High dose of magnesium… measure excretion in urine

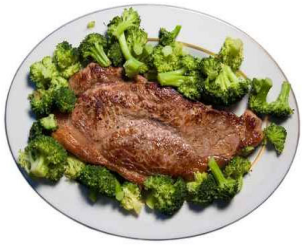
Iron

- Mineral involved in many physiological processes
  - Oxygen transport, formation of blood cells, energy metabolism
  - Anemia - common manifestation of iron deficiency
- Iron most common nutrient deficiency in world
  - Adversely affects 2 billion people worldwide
  - Symptoms: anemia, low energy, fatigue, difficulty concentrating
  - Iron supplements resolve deficiency... common side effects
    - Constipation, nausea, etc.



Iron

- Dietary sources
  - Heme iron – red meat (grass-fed)
  - Non-heme iron – beets, beans



- Test iron levels before supplementing
  - Deficiency common… but excess iron also problematic
  - *Regularly donate blood!* Morley Robbins work
  - Especially men & post-menopausal women
    - Iron lost through menstruation
  - Consider *TF, TFR2* SNPs

Choline

- Choline – key cell membrane component
  - Not technically vitamin, but considered essential nutrient
  - Role in methylation, neurotransmitter production, folate metabolism
    - Found in egg yolks, liver, animal protein, beets, leafy greens
  - Improves memory & prevents cognitive decline in older adults 98% post-menopausal women inadequate choline intake
    - Fioravanti (2005) *Cochrane Database Syst Rev.* 2:CD000269.
    - Gestuvo (2012) *Aging Health* 8(1):89-97.

Choline and Eggs

- Are eggs healthy? DEPENDS ON THE EGG

≠

Risk of salmonella, very high omega-6, less nutrients in yolk

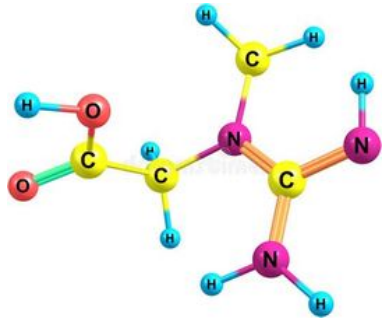
Less risk of salmonella, higher omega-3, more nutrients in yolk

Choline and Eggs

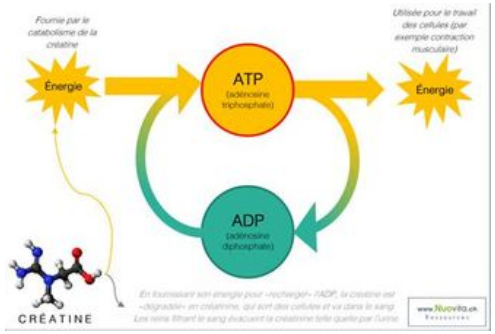
Other Nutrients of Interest

Creatine

- Peptide - arginine, glycine, methionine
  - Creatine phosphate molecule in cells
  - Primarily in muscle (including heart)
  - Endogenous synthesis… resource intensive

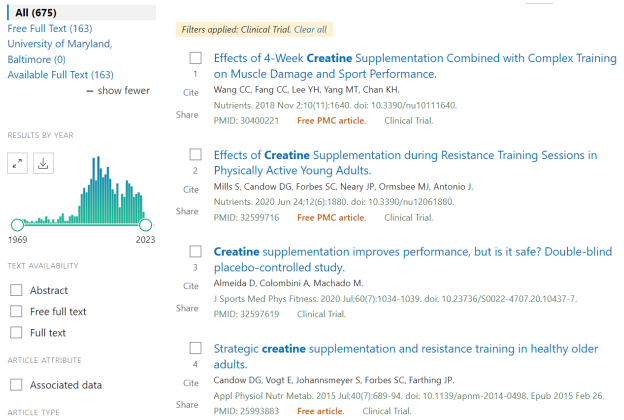


- Donates phosphate to ADP… regenerates ATP
  - Increases body energy stores



Creatine

- Dietary sources of creatine
  - Beef (5 grams per kg)
  - Chicken
  - Cold-water fish (e.g. herring, salmon)
  - Small amount in dairy
- Creatine monohydrate supplementation
  - One of best studied supplements
    - Increase muscle strength
    - Increase lean body mass
    - Increase testosterone
    - Improve cognitive function… particularly in vegetarians
    - Reduce fatigue
    - Reduce depressive symptoms

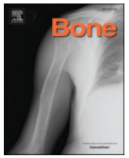


Creating and Aging

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Creatine supplementation for older adults: Focus on sarcopenia, osteoporosis, frailty and Cachexia

Darren G. Candow [a,*], Philip D. Chilibeck [b], Scott C. Forbes [c], Ciaran M. Fairman [d], Bruno Gualano [e], Hamilton Roschel [e]

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ARTICLE INFO

Keywords:
Muscle
Strength
Bone
Falls
Disease

ABSTRACT

Sarcopenia refers to the age-related reduction in strength, muscle mass and functionality which increases the risk for falls, injuries and fractures. Sarcopenia is associated with other age-related conditions such as osteoporosis, frailty and cachexia. Identifying treatments to overcome sarcopenia and associated conditions is important from a global health perspective. There is evidence that creatine monohydrate supplementation, primarily when combined with resistance training, has favorable effects on indices of aging muscle and bone. These musculoskeletal benefits provide some rationale for creatine being a potential intervention for treating frailty and cachexia. The purposes of this narrative review are to update the collective body of research pertaining to the effects of creatine supplementation on indices of aging muscle and bone (including bone turnover markers) and present possible justification and rationale for its utilization in the treatment of frailty and cachexia in older adults.

Creatine and Aging

nutrients

MDPI

Review

Meta-Analysis Examining the Importance of Creatine Ingestion Strategies on Lean Tissue Mass and Strength in Older Adults

Scott C. Forbes [1,*], Darren G. Candow [2], Sergej M. Ostojic [3], Michael D. Roberts [4] and Philip D. Chilibeck [5]

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* Correspondence: forbess@brandonu.ca; Tel.: +1-204-727-9637

Abstract: Creatine supplementation in conjunction with resistance training (RT) augments gains in lean tissue mass and strength in aging adults; however, there is a large amount of heterogeneity between individual studies that may be related to creatine ingestion strategies. Therefore, the purpose of this review was to (1) perform updated meta-analyses comparing creatine vs. placebo (independent of dosage and frequency of ingestion) during a resistance training program on measures of lean tissue mass and strength, (2) perform meta-analyses examining the effects of different creatine dosing strategies (lower: ≤5 g/day and higher: >5 g/day), with and without a creatine-loading phase (≥20 g/day for 5–7 days), and (3) perform meta-analyses determining whether creatine supplementation only on resistance training days influences measures of lean tissue mass and strength. Overall, creatine (independent of dosing strategy) augments lean tissue mass and strength increase from RT vs. placebo. Subanalyses showed that creatine-loading followed by lower-dose creatine (≤5 g/day) increased chest press strength vs. placebo. Higher-dose creatine (>5 g/day), with and without a creatine-loading phase, produced significant gains in leg press strength vs. placebo. However, when studies involving a creatine-loading phase were excluded from the analyses, creatine had no greater effect on chest press or leg press strength vs. placebo. Finally, creatine supplementation only on resistance training days significantly increased measures of lean tissue mass and strength vs. placebo.

Keywords: supplements; hypertrophy; sarcopenia

check for updates

Citation: Forbes, S.C.; Candow, D.G.; Ostojic, S.M.; Roberts, M.D.; Chilibeck, P.D. Meta-Analysis Examining the Importance of Creatine Ingestion Strategies on Lean Tissue Mass and Strength in Older Adults. *Nutrients* **2021**, *13*, 1912. https://doi.org/10.3390/nu13061912

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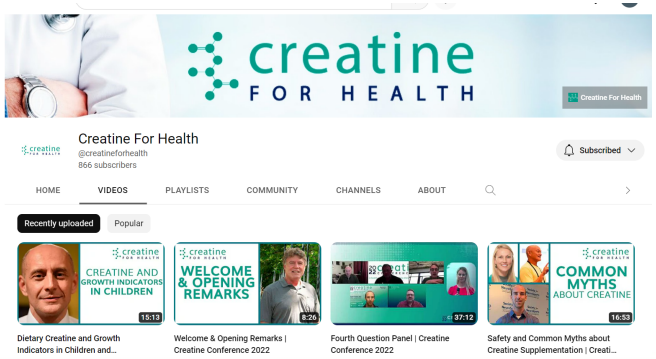
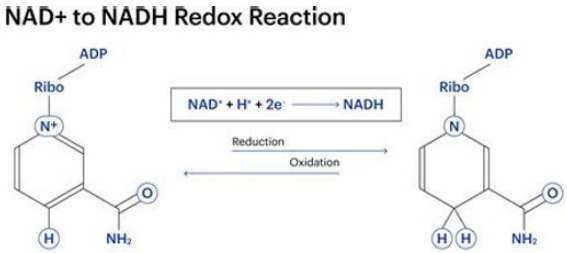
Creatine and Aging

- *Practical tips*
  - “Loading” helpful for strength and lean body mass
    - 10-20 grams/day for week… 5 grams per day afterwards
    - Not necessary for most other conditions
  - Best effects on lean body mass with resistance training
  - Supplementation important if limited red meat in diet
  - Versatile supplement for most people



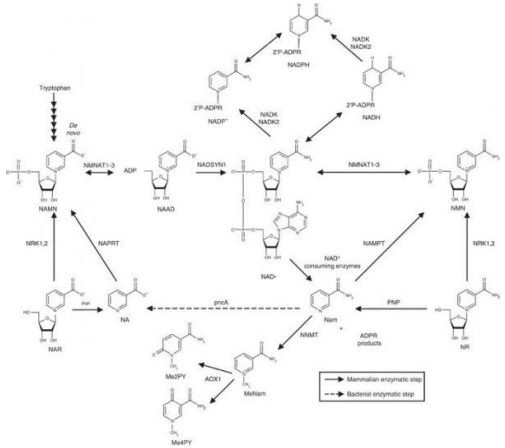
NAD+ Precursors

- Nicotinamide Adenine Dinucleotide (NAD)
  - Coenzyme: electron transfer... mitochondrial function, DNA repair, immune function, cell signaling, gene expression, senescence
    - Hallmarks of aging
  - Synthesized in three pathways
    - 1. de novo, 2. Preiss-Handler, 3. salvage
  - NAD+ oxidized form, NADH reduced form
  - Altered NAD+ homeostasis in many diseases
    - Neurodegenerative disease, CVD, diabetes, cancer
    - Decreased synthesis with age



NAD+ Precursors

- Oral NAD+ delivery does not increase NAD+
  - Intestinal effect of NAD+ lowers bioavailability & large polarity of inhibits transport through plasma membrane
- NAD+ precursors
  - Dietary tryptophan… farthest upstream factor
    - Sources: poultry, fish, eggs, dairy, soy
  - Nicotinamide (NAM) – form of niacin (B3)
    - Aka niacinamide
  - Nicotinic acid (NA) – form of niacin (B3)
  - **Nicotinamide riboside (NR)**
  - **Nicotinamide mononucleotide (NMN)**



NAD+ Precursors

Aging Dis. 2021 Dec; 12(8): 1879–1897.
Published online 2021 Dec 1. doi: 10.14336/AD.2021.0523
PMCID: PMC8612620
PMID: 34881075

Pharmacology and Potential Implications of Nicotinamide Adenine Dinucleotide Precursors

Jing She, Rui Sheng, * and Zheng-Hong Qin *

Abstract

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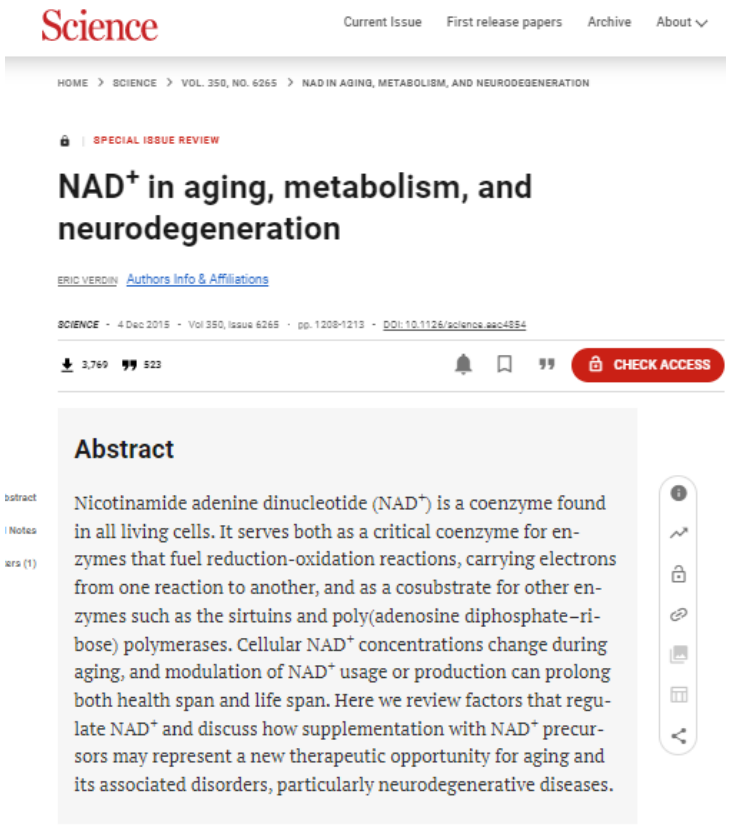
Coenzyme I (nicotinamide adenine dinucleotide, NAD^+/NADH) and coenzyme II (nicotinamide adenine dinucleotide phosphate, $NADP^+$/NADPH) are involved in various biological processes in mammalian cells. NAD^+ is synthesised through the de novo and salvage pathways, whereas coenzyme II cannot be synthesised de novo. NAD^+ is a precursor of coenzyme II. Although NAD^+ is synthesised in sufficient amounts under normal conditions, shortage in its supply due to over consumption and its decreased synthesis has been observed with increasing age and under certain disease conditions. Several studies have proved that in a wide range of tissues, such as liver, skin, muscle, pancreas, and fat, the level of NAD^+ decreases with age. However, in the brain tissue, the level of NADH gradually increases and that of NAD^+ decreases in aged people. The ratio of NAD^+/NADH indicates the cellular redox state. A decrease in this ratio affects the cellular anaerobic glycolysis and oxidative phosphorylation functions, which reduces the ability of cells to produce ATP. Therefore, increasing the exogenous NAD^+ supply under certain disease conditions or in elderly people may be beneficial. Precursors of NAD^+ have been extensively explored and have been reported to effectively increase NAD^+ levels and possess a broad range of functions. In this review article, we discuss the pharmacokinetics and pharmacodynamics of NAD^+ precursors.

Keywords: NAD^+, NA, NAM, NMN, NR, aging

NAD+ Precursors



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HOME > SCIENCE > VOL. 350, NO. 6265 > NAD IN AGING, METABOLISM, AND NEURODEGENERATION

SPECIAL ISSUE REVIEW

NAD^+ in aging, metabolism, and neurodegeneration

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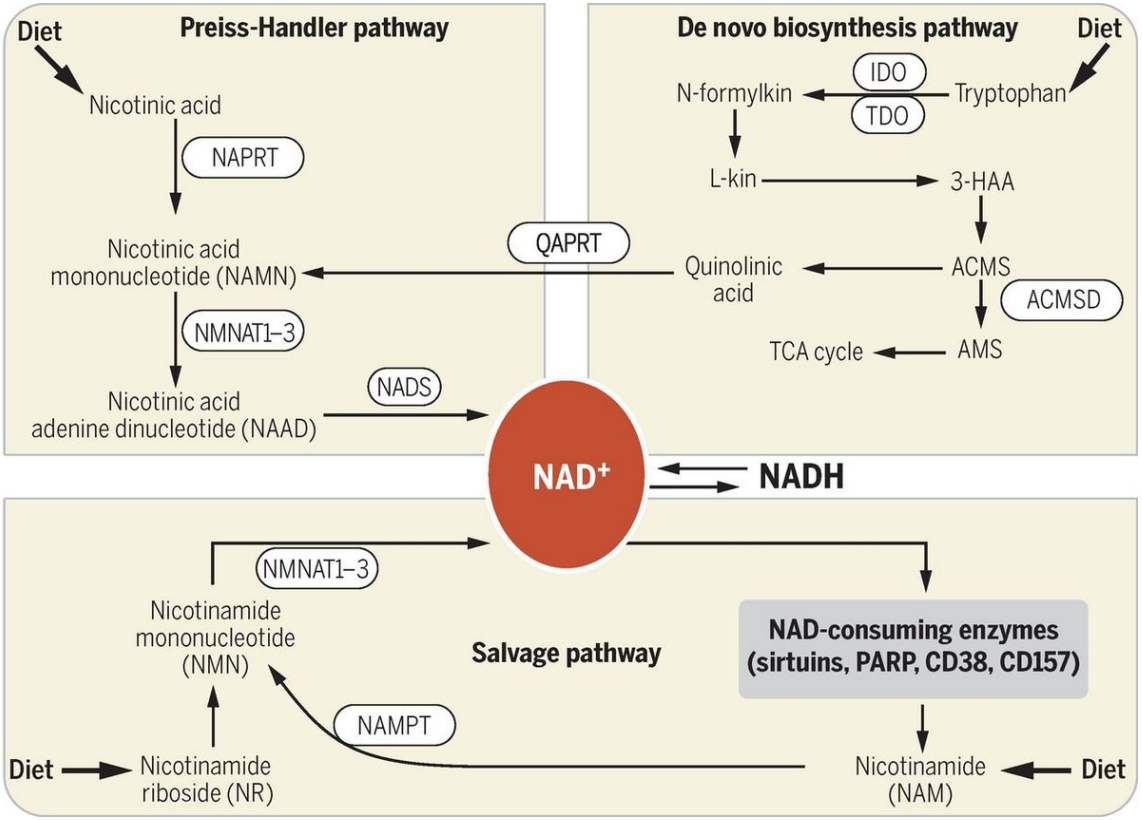
Abstract

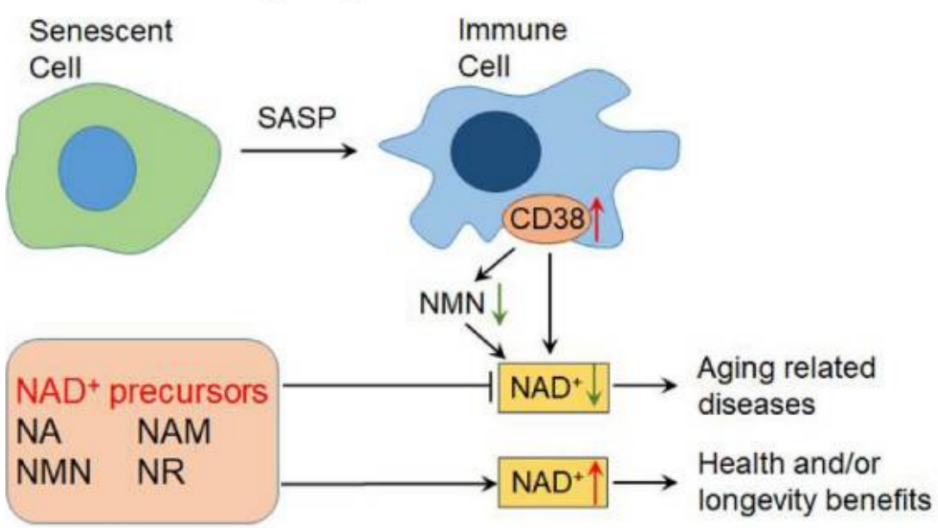
Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme found in all living cells. It serves both as a critical coenzyme for enzymes that fuel reduction-oxidation reactions, carrying electrons from one reaction to another, and as a cosubstrate for other enzymes such as the sirtuins and poly(adenosine diphosphate–ribose) polymerases. Cellular NAD^+ concentrations change during aging, and modulation of NAD^+ usage or production can prolong both health span and life span. Here we review factors that regulate NAD^+ and discuss how supplementation with NAD^+ precursors may represent a new therapeutic opportunity for aging and its associated disorders, particularly neurodegenerative diseases.

NAD+ Precursors



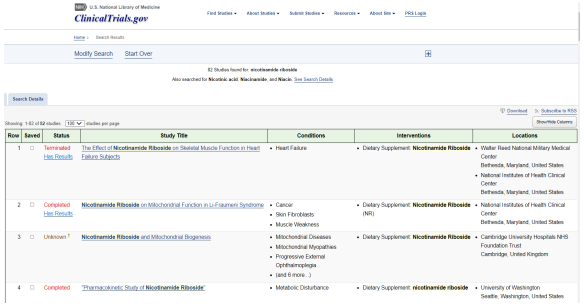
NAD+ Precursors

- NAD+ levels regulated by CD38 enzyme
  - CD38 increase with senescent cells… due to senescent cells increasing inflammation (SASP)
  - Upstream CD38 inhibitors… potential of apigenin?



NAD+ Precursors: Evidence

- Majority preclinical studies



- NR clinical trials
  - 82 results in ClinicalTrials.gov
  - Positive findings: NAD+ in blood, Parkinson's disease, brown adipose tissue (mitochondrially-dense), body composition

- NMN clinical trials
  - 19 results in ClinicalTrials.gov
  - Positive findings: NAD+ in blood,. improved physical performance, reduced fatigue, weight loss, improved insulin sensitivity

NAD+ Precursors

- *Practical tips*
  - No flushing with NR and NMN
    - Common effect with niacin supplementation
  - NR vs. NMN… unclear
    - More human clinical studies on NR
    - NMN access potentially limited by FDA
  - Consume with methyl donor
    - Trimethylglycine (TMG)… in some dietary supplements
  - Potential synergy with sirtuin activators
    - Resveratrol, pterostilbene, etc.
  - Caution if active cancers/potentially family history
  - Likely not necessary for younger adults

Summary

- Nutrition critical role in optimal aging & healthspan
- Nutrient demands increase with aging
  - Physiological changes, social/lifestyle factors, age-related disease, polypharmacy
- Foundation: nutrient dense diet
  - High in bioavailable protein, omega-3 fats & micronutrients
- Many supplements can fill gaps in nutrient demands
  - High-quality multivitamin, omega-3 fats, micronutrients (based on tests/symptoms), creatine monohydrate, NAD+ precursors

Thank you!

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