Unloading-induced atrophy is a relatively uncomplicated form of muscle loss. Most of the loss of muscle mass during disuse atrophy can be accounted for by a depression in the rate of protein synthesis. Whereas in disease states associated with inflammation (cancer cachexia, AIDS, burns, sepsis, and uremia), there is a procatabolic hormonal and cytokine environment.

...procatabolic hormonal and cytokine environment...
It is imperative that these studies include examination of dynamic measures of muscle protein turnover and putative metabolic controllers... unless we have a clear idea of the basic responses to immobilization per se, the effects of such factors will not be easily teased out and therapeutic goals will remain largely unattainable.

Hypercatabolism

Hyper-catabolic conditions associated with proteolysis:
- Cancer cachexia
- Cachexia associated with heart failure
- Sepsis
- Starvation
- Metabolic acidosis
- Stress/trauma associated with excess glucocorticoids
- Space flight

n3/EPA and Muscle

Eicosapentaenoic acid (EPA)
- 20-C, omega-3 fatty acid
- Dietary sources: fish oil, flaxseed, walnuts

Beneficial effects on cholesterol, lipid metabolism, and cardiovascular health
Omega-3 and Cancer

Proportion of tumor-bearing rats

Vanamala et al., Carcinogenesis, 2008

Vitamin D

Sources
- UVB radiation
- Food
  - Seafood, mushrooms, egg yolk, fortified foods

Nomenclature
- Vitamin D$_2$ (ergocalciferol)
- Vitamin D$_3$ (cholecalciferol)
- 25-OH vitamin D
- 1,25 (OH)$_2$ vitamin D

RDA (1997 IOM)
- 19-50 y: 200 IU/d
- 50-70 y: 400 IU/d

The 2005 Dietary Guidelines for Americans recommendation advised older adults, people with dark skin, and people exposed to insufficient sunlight to consume 1000 IU/d.

Contributing Factors to Vitamin D Status
- Age
- Ethnicity
- Salt-sensitive hypertension
  - Increased protein excretion in salt-sensitive individuals and Dahl rats with salt loading
- Adiposity/obesity
Vitamin D is associated with:
- Calcium metabolism
- Fracture Risk/BMD
- Cardiovascular health
- Immune function
- Multiple Sclerosis
- Dementia
- Parkinson’s Disease
- Tuberculosis
- Incidence of C-section
- The common cold

Vitamin D status has been related to:
- Fractures, fracture risk, BMD
- Muscle strength/function, falls
- Cancer (prostate, breast, colon)
- Multiple sclerosis
- Blood pressure/heart disease
- Diabetes (type 1)

Recommendations
- Encourage adequate vitamin D:
  - Intake
    - Fortified milk, orange juice
    - Fish (salmon, tilapia, tuna)
    - Few other sources...
  - Sunlight
  - Supplements

...the criterion for broad-based supplementation in the general population is not fulfilled, except for in high risk groups, such as the elderly...all other persons with negligible exposure to sunshine.

Space Food

<table>
<thead>
<tr>
<th>Food</th>
<th>VE D (IU)</th>
<th>Flight Requirement (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon</td>
<td>396</td>
<td>450</td>
</tr>
<tr>
<td>Tuna</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Breakfast Drink</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Tuna Noodle Casserole</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Cornflakes</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Tuna Salad Spread</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Bran Chex</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Scrambled Eggs</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Bread Pudding</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Granola w/Raisins</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Tapioca Pudding</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Teriyaki Beef</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Pork Chops</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Vegetable Quiche</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Poutine Soup</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>
Upper Limits

2000 IU/day is currently defined IOM no observed adverse events limit (NOAEL). Studies of higher levels have proven safe...

Sunlight does not result in toxicity

Watch multivitamins (vit A and other nutrients may be in excess)

Stability Study

Vitamin D status goes down after long-duration spaceflight.

Questions:
  - Is the stability of vitamin D in the food system and supplement different during spaceflight?
  - Is the daily dose not high enough to maintain status?
  - Does vitamin D metabolism change during spaceflight?

Stability Study

Stability of vitamin D in food/supplement is not altered during spaceflight

Question:
  - Is the daily dose simply not high enough to maintain status in an environment with no sun exposure?
3 levels of vitamin D supplementation:
- 400 IU/d (n = 18)
- 1000 IU/d (n = 19)
- 2000 IU/d (n = 18)

3 blood collections and diet logs
- 25D, 1,25D, PTH, Ca, VDBP, NTX

Double blinded supplementation (Smith et al., 2009)

Compliance
- 84% on average

Vitamin D status is related to body weight…
- what if we exclude subjects with BMI >29 kg/m²?

1000 or 2000 IU/d was enough to reach 80 nmol/L and maintain vitamin D status

Residual Questions…
- Could compliance be improved with a weekly dose instead of a daily dose?
- Is vitamin D status related to observed changes in immune function during polar winters?
In addition to BMI, the efficacy of vitamin D supplementation is affected by baseline status.

Compliance:
- 2000 IU/d: 91%
- 10,000 IU/wk: 97%

Residual Questions...

Is a higher, less frequent dose as effective as a daily or weekly dose? Does a high dose result in a high serum concentration of 25-OH vitamin D (or metabolites) or alter serum or urine calcium?

Vitamin D Dosing Study

- 2000 IU/d
- 10,000 IU/wk
- 50,000 IU weekly x4; then 1/mo

Vit D (and metabolites)
Ca, etc.
Dist. ux
Vitamin D Dosing Study

Baseline

60 Days

1 subject in 2000 IU/d group had 2 values >150 nmol/L.
2 subjects in 50000 IU group had 3-5 values > 150 nmol/L.

Urine Ca

Nutrition SMO

Calcium

[Diagram of the human body showing calcium pools and processes like absorption, secretion, deposition, and resorption]
Collagen Crosslinks

Bone Resorption

Space Flight:
- Urinary collagen xlinks
- Urinary Ca
- Urinary OH-Proline V_{Ca}
Bone resorption is increased during flight

Bone Formation/Resorption

Calcium Isotopes

Calcium Isotopes

Higher \( \delta^{44}\text{Ca} \) = "heavier"
Lower \( \delta^{44}\text{Ca} \) = "lighter"
Regenerative ECLSS

URINE PROCESSOR ASSEMBLY

Recycle Filter Tank Assembly
Distillation Assembly

UPA

Urine Calcium

Urine Volume

-17%
Current folate intakes do not maintain folate status

How much folate is in the food? If enough – then:

Is folate stable on orbit? If it is – then:

What is changing?
Vitamin K

Fluid Intake

Fluid Shift

Renal Stone Risk

Nutrition SMO

UMS
Excess sodium intake (and related effects on acid/base physiology) is associated with a number of health issues:

- Bone loss
- Increased renal stone risk
- Impaired muscle performance/protein catabolism
- Altered glucose metabolism
- Altered vitamin D metabolism
- Hypertension

With the exception of hypertension, all of these other factors have been raised as concerns for space travelers.

High sodium has been shown in bed rest (and ambulatory) studies to exacerbate bone breakdown (Heer, et al.)

Excess sodium intake leads to non-osmotic (i.e., non-fluid retaining) storage of sodium, which is bound to glycosaminoglycans in skin, exchanging with a hydrogen ion. The excess sodium is bound to glycosaminoglycans in skin, exchanging with a hydrogen ion.
Acidosis

Recap 3

- The higher the acid load and the heavier you are, the more your renal function and the higher the body's acid-base balance.
- Typical recommendations are low in alkali content.
- Excess dietary sodium can lead to increased Na+/H+ exchange in skin GAGs, which affects Na+ excretion.
- Excess dietary sodium has implications for bone health.

Iron (RBCs, and oxidative damage)

Iron and Oxygen

Radiation/oxygen issues have implications for cataracts and other health issues.

Total Body Iron

Males

Females
Iron and Oxidative Damage

Bed Rest

NEEMO

Supplements

Outliers

EVA Pilot Study

**Table:**

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grape juice</td>
<td>10.5</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0.1</td>
</tr>
<tr>
<td>NAC</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Graphs:**

- Iron and Oxidative Damage
- Bed Rest
- NEEMO
- Supplements
- Outliers
- EVA Pilot Study

**Data Points:**

- 8OHdG (ng/mmol creat)
- Total body iron (%)
- Transferrin receptors (%)
- SOD (U/g hgb)
- MDA (%)
- Total body iron (mg/kg)
- Total antioxidant capacity
- Phylloquinone (nmol/L)
- 25(OH) Vitamin D (nmol/L)
- Vitamin C (ug/mL)
- Serum Folate (% Change)
- Max Voluntary Contraction
- Endurance - Reps

**References:**

Zwart et al., *Aviat Space Environ Med*, 2009
Zwart et al., *J Nutr*, 2009
Bone Resorption

% from baseline

Week of Bed Rest

Pre Measure

FD15

FD30

FD60

FD120

FD180

R+0

R+30

NTX (% change)

Artificial Gravity.1

Nutrition

Exercise

Potential Countermeasures

Pharmacology

Gravity

Smith et al., J Appl Physiol, 2009

Exercise Countermeasures

Bone Resorption

CON

AG

Smith et al., JBMR, 2003

Shackelford et al., JAP, 2004

Smith et al., Bone 2008
Dietary protein increases urinary calcium
Oxidation of excess protein yields acid ($H^+, H_2SO_4$)
  - Renal buffering
  - Bone: reservoir of base
Osteoclasts are more active at lower pH
Excess protein: beneficial or harmful to bone?
  - Many factors influence the net effect

Animal protein
Diets rich in animal protein tend to have greater overall acid potential
Renal net acid excretion

Vegetables/fruits
Also contain substantial amounts of base precursors (and K)
APro/K provides an estimation of acid/alkali load
Pro K

Controlled dietary intake
High or Low APro:K
Monitored dietary intake

Blood/Urine markers

EXAMPLE Menu

High APro/K Day 1 Example

<table>
<thead>
<tr>
<th>Breakfast</th>
<th>Fruit and Yogurt</th>
<th>Spinach Omelet</th>
<th>Whole Grain Bagel</th>
<th>Chia Pudding</th>
<th>Fresh Fruit</th>
<th>Fresh Juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunch</td>
<td>Chicken Salad</td>
<td>Turkey Meat</td>
<td>Brown Rice</td>
<td>Brownie</td>
<td>Yogurt</td>
<td>Soy Milk</td>
</tr>
<tr>
<td>Dinner</td>
<td>Spaghetti</td>
<td>Grilled Salmon</td>
<td>Grilled Vegetables</td>
<td>Cheese</td>
<td>Fish &amp; Chips</td>
<td>Pudding</td>
</tr>
</tbody>
</table>

Low APro/K Day 1 Example

<table>
<thead>
<tr>
<th>Breakfast</th>
<th>Vegetarian Omelet</th>
<th>Vegetable Sauce</th>
<th>Brown Rice</th>
<th>Tofu Pudding</th>
<th>Fresh Fruit</th>
<th>Fresh Juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunch</td>
<td>Lentil Soup</td>
<td>Vegetable Stew</td>
<td>Grilled Veggie</td>
<td>Almond Milk</td>
<td>Yogurt</td>
<td>Soy Milk</td>
</tr>
<tr>
<td>Dinner</td>
<td>Grilled Chicken</td>
<td>Pork Chops</td>
<td>Pasta</td>
<td>Cheese</td>
<td>Fish &amp; Chips</td>
<td>Pudding</td>
</tr>
</tbody>
</table>

NOTE: the low ratio diet is NOT low protein, and NOT vegetarian

NOTE: the pattern above (red or blue) is an example, your pattern may vary

Blood/Urine (24-h F; 48-h G) will be collected at the end of each session, and on L-10 and R+5.
Acid/Base and Bone

High protein, low potassium diet

Acid Load >> Alkali Load

\[ H^+ \text{excess} \rightarrow \text{Organic anions} \]

\[ \text{Na}^+/\text{H}^+ \text{exchange in skin GAGs} \]

\[ \text{Excess dietary sodium} \]

Inflammation

Bed rest
Hindlimb unloading
Spaceflight
Ionizing radiation/UVC

NF-κB
κB Inhibitor

Arachidonic acid
PIF
LPS
RANKL
TNF-α

NF-κB (active)

↓ Muscle proteolysis

骨细胞分化

骨吸收

Inflammatory Markers

NF-κB (active)

↓ Muscle proteolysis

骨细胞分化

骨吸收

Inflammation/Bone

↓ Bone resorption

MTX (nmol/d)

TNF-α (pg/mL)