Protein (and muscle)
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. .....
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 upregulation of the ubiquitin-proteasome system:
- Cancer cachexia (Lorte et al. 2001; Tisdale et al. 2009)
- Cachexia associated with heart failure (Filippatos et al. 2005, Freeman et al. 2005)
- Sepsis (Visin et al. 1996; Tiao et al. 1994)
- Starvation (Whitehouse, 2001)
- Metabolic acidosis (Mitch et al. 1994)
- Stress/trauma associated with excess glucocorticoids (Wing et al. 1993, Bolli et al. 2000)
- Space flight (Ikemoto et al. 2001; Riley et al. 1992)

- 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

Vitamin D Intake Guidelines

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.

Vitamin D: Review

Other metabolites:
24,25(OH)2D3
25,26(OH)2D3
35 others…

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

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

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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

Smith et al., J Nutr, 2006
Smith et al., J Nutr, 2005

SN
Control
Pre flight
Post flight

25 (OH) Vitamin D (nmol/L)

0
10
20
30
40
50
60
70
80
90
100
25 (OH) Vitamin D (nmol/L)

0
10
20
30
40
50
60
70
80
90
100

Calcium metabolism
Fracture Risk/BMD
Muscle strength/function
Cancer
Cardiovascular health
Immune function
Diabetes
Multiple Sclerosis
Dementia
Parkinson’s Disease
Tuberculosis
Incidence of Csection

The common cold

Vitamin D and PTH
Erkal, Osteo Int, 2006
Thomas et al., NEJM, 1998
Chapuy et al., Osteo Int, 1997

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)

Bischoff-Ferrari, Am J Clin Nutr, 2006

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>VI D (IU)</th>
<th>Flight Requirement (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meal</th>
<th>Vit D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon</td>
<td>396</td>
</tr>
<tr>
<td>Tuna</td>
<td>152</td>
</tr>
<tr>
<td>Breakfast Drink</td>
<td>116</td>
</tr>
<tr>
<td>Tuna Noodle Casserole</td>
<td>96</td>
</tr>
<tr>
<td>Cornflakes</td>
<td>68</td>
</tr>
<tr>
<td>Tuna Salad Spread</td>
<td>64</td>
</tr>
<tr>
<td>Bran Chex</td>
<td>68</td>
</tr>
<tr>
<td>Scrambled Eggs</td>
<td>64</td>
</tr>
<tr>
<td>Bread Pudding</td>
<td>64</td>
</tr>
<tr>
<td>Granola w/Raisins</td>
<td>44</td>
</tr>
<tr>
<td>Tapioca Pudding</td>
<td>44</td>
</tr>
<tr>
<td>Teriyaki Beef</td>
<td>36</td>
</tr>
<tr>
<td>Pork Chops</td>
<td>32</td>
</tr>
<tr>
<td>Vegetable Quiche</td>
<td>28</td>
</tr>
<tr>
<td>Pasta Soup</td>
<td>28</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).

Vitamin D Toxicity

Hypercalcemia, hypercalciuria, soft tissue calcification, kidney stones

Vitamin D

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

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?
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?
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.

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.

Nutrition SMO

Calcium
**Collagen Crosslinks**

- **N-Telopeptide**
  - Increased in flight

**Bone Resorption**

- **Urinary collagen xlinks**
- **Urinary Ca**
- **Urinary OH-Proline**

**Bone resorption is increased during flight**

**Bone Formation/Resorption**

- **BSAP** (% change from baseline)

**Calcium Isotopes**

- Higher $\delta^{44}\text{Ca} = "heavier"$
- Lower $\delta^{44}\text{Ca} = "lighter"$

$$\delta^{44}\text{Ca} = \left( \frac{^{44}\text{Ca}}{^{40}\text{Ca}} \right)_{\text{sample}} \times 1000$$

- Skulan et al., Clin Chem, 2007

**Calcium Isotopes**

- 40Ca 42Ca 43Ca 44Ca 46Ca 48Ca
  - 97% 0.65% 0.11% 2.09% 0.004% 0.19%

Smith et al., JCEM, 1998
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.

In 2005-2006, the average US intake of Na was estimated at 3,436 mg Na/d.*

In 1990-1999, the average US intake of Na was estimated at:
- 3,377 mg for 31-50 yo M
- 3,539 mg for 31-50 yo F

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

**Note:** This is the basis for the ESA sponsored SOLO experiment on ISS.
Acidosis

From Dr. L. Frassetto (UCSF) 10/6/09 JSC presentation

Acid/Base and Bone

Excess dietary sodium

Iron (RBCs, and oxidative damage)

Iron and Oxygen

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

Total Body Iron
**Bone Formation**

Bone formation is illustrated with graphs showing changes in bone mass over time. The graphs compare bone formation in control and exercise groups. The data is sourced from Smith et al., JBMR, 2003; Shackelford et al., JAP, 2004; Smith et al., Bone 2008; LeBlanc et al., JMNI, 2002.

**Nutrition and Bone**

Nutrition and bone health are depicted with images of food items, emphasizing the importance of a balanced diet.

**Bisphosphonates**

Graphs showing the effects of bisphosphonates on bone density over time. The graphs compare control and bisphosphonate treatment groups.

**Nutrition and Bone**

Nutrition and bone health are highlighted with images of food items, underscoring the role of diet in bone health.

**Vitamin K**

A visual representation of SOLO (Serotonin 2C3O4 Linked) with graphs showing the effects of vitamin K supplementation on bone density.

**Dietary Protein**

Dietary protein increases urinary calcium and can be detrimental to bone if it is not balanced. Oxidation of excess protein yields acid, which can negatively affect bone density. Renal buffering and bone reservoir of base play a role. Osteoclasts are more active at lower pH.

**Animal vs. Vegetable**

Animal protein, rich in animal protein, tends to have a greater overall acid potential and renal net acid excretion. Vegetables/fruits also contain substantial amounts of base precursors (and K). APro/K provides an estimation of acid/alkali load.
APRO:K and Bone

Pro K

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

Blood/Urine markers

EXAMPLE Menu

Nutrition and Bone

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