New news about protein

HOW MUCH IS TOO MUCH... AND NOT ENOUGH

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PROTEIN TRENDS & TECHNOLOGIES SEMINAR

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Objectives of today’s presentation

- Review the basics regarding protein and amino acids
- Describe how scientists estimate how much protein is required by the body each day
- Highlight new research on protein requirements of different populations (Is the protein RDA enough?)
- Compare protein intakes in different populations with existing and proposed protein requirements
  - Does it make a difference?
- Discuss the issue of how much protein is too much protein in the diet
Basics of protein
Functions of proteins in the body

- **Enzymes**
  - All biological enzymes are made of protein
    - For example, the digestive enzymes trypsin and amylase
- **Hormones (some)**
  - Insulin and glucagon
  - Not all hormones are proteins
    - Testosterone is a steroid
- **Structural**
  - Actin & myosin (muscle)
  - Collagen (skin)
Functions of Proteins (cont’d)

- Immunologic
  - All antibodies

- Transport and storage
  - Carriers of fatty acids, oxygen (hemoglobin), iron, vitamin A, copper, and other nutrients
  - Cholesterol and triglycerides carried by lipoproteins

- pH buffering
  - In blood, muscle, essentially everywhere

- Energy source
  - When carbohydrates are limited (gluconeogenesis)
The basics about protein and amino acids

- The proteins in our foods and in our bodies are made up of individual building block units known as amino acids.
- The chemical bonding of amino acids together forms a peptide.
- When the number of amino acid units bonded together becomes really large (e.g., 50 or more), we refer to the molecule as a protein.
- At right is a dipeptide of two amino acids bonded together.
There are 20 amino acids that make up the protein in our foods.

Body proteins also comprise different combinations of these 20 amino acids.

Classifications of amino acids in the body:

- **Indispensable**: must be obtained from the diet each day
- **Dispensable**: can be produced in the body, dietary source not required
- **Conditionally indispensable**: dietary source required only under certain circumstances
### Classifications of amino acids relative to human requirements

<table>
<thead>
<tr>
<th>Indispensable</th>
<th>Dispensable</th>
<th>Conditionally indispensable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>Alanine</td>
<td>Arginine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Aspartic acid</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Leucine</td>
<td>Asparagine</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Lysine</td>
<td>Glutamic acid</td>
<td>Glycine</td>
</tr>
<tr>
<td>Methionine</td>
<td>Serine</td>
<td>Proline</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td></td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Threonine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complete vs. incomplete proteins

- Complete proteins: All of the essential amino acids in the right amounts to support human growth and development

- Incomplete proteins: One or more essential amino acids that are too low to support human growth and development if that protein was to be the sole source of protein in the diet

- Ways to get enough complete protein in your diet:
  - Most animal proteins are complete proteins
  - Soy is also a high quality protein
  - Consuming a variety of vegetable proteins each day can be helpful for vegetarians
    - Grains typically low in lysine, high in methionine
    - Legumes typically low in methionine, high in lysine
    - Consume both throughout the day
Protein Digestion

Gastric phase (stomach)

- Hydrochloric acid (HCl) from cells in stomach unfolds protein
- Pepsinogen (chief cells) → HCl → Pepsin (enzyme)
- Pepsin digests proteins → Large peptide fragments

Small intestine phase

- Cholecystokinin (hormone released in upper small intestine) triggers pancreas to secrete digestive enzymes once digestion products leave the stomach
- Digestive enzymes are activated and continue to break down peptides into di-/tri-peptides and free amino acids, which are taken up by intestinal cells

Amino Acid and Peptide Absorption

- Intestinal cells have various transport proteins at both the luminal side and the blood side to give AAs and peptides access to the circulation.

- **COMMON MYTH:** The body can only digest 20-30 g protein at one time.

  - There is a key difference between digestion/absorption and utilization of amino acids by muscles.

What happens to amino acids after they are absorbed?

Dietary intake → Free amino acids

Excretion → Oxidation → Non-protein pathways → AA Synthesis (dispensable)

Tissue Protein

Synthesis → Degradation

Protein losses → Skin, Hair, Feces

Muscle Protein Turnover

- There is a constant flux between making new muscle protein and breaking down old muscle protein
  - Known as “protein turnover”
- Goal for increasing muscle size is for muscle protein synthesis to exceed breakdown

Can protein give you energy?

- Yes, BUT this is not preferred and generally occurs only to a limited extent
- DOWNSIDE: The body can’t use the nitrogen group for energy and must get rid of it (Deamination)
- The nitrogen group is converted to urea in the liver and then excreted in urine
- Excretion products of protein oxidation such ammonia and, to a lesser extent, urea, have potential toxicity to the body
Protein requirements and recommendations

IS THE RECOMMENDED DIETARY ALLOWANCE (RDA) FOR PROTEIN ENOUGH?
Definition of the Recommended Dietary Allowance (RDA)

- “The average daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group.”

- The RDA for protein is expressed as grams per kg of body weight per day

- NOTE: To convert your body weight from pounds to kg, divide your weight in pounds by 2.2

- 110 lb = 50 kg
- 132 lb = 60 kg
- 154 lb = 70 kg
- 176 lb = 80 kg
- 198 lb = 90 kg
- 220 lb = 100 kg

Protein RDAs by gender and life stage (g/kg body weight/d)  

<table>
<thead>
<tr>
<th>Life stage group</th>
<th>Male RDA</th>
<th>Female RDA</th>
<th>Adequate Intake (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td></td>
<td></td>
<td>1.52</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1-3 y</td>
<td>1.05</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>4-8 y</td>
<td>0.95</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>9-13 y</td>
<td>0.95</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>14-18 y</td>
<td>0.85</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>19-30 y</td>
<td>0.80</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>31-50 y</td>
<td>0.80</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>51-70 y</td>
<td>0.80</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>0.80</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td>1.10</td>
</tr>
<tr>
<td>Lactation</td>
<td></td>
<td></td>
<td>1.30</td>
</tr>
</tbody>
</table>

Nitrogen balance studies: basis for the protein RDA

- The nitrogen balance study is a classical technique for estimating human protein requirements
- Attempts to measure the balance between nitrogen intake (diet) and nitrogen losses from the body
- Nitrogen balance means that the amounts of nitrogen intake and losses from the body are the same (maintenance)
  - Growth: Positive nitrogen status (N intake > losses)
  - Catabolism: Negative nitrogen status (N intake < losses)
A new method: Indicator Amino Acid Oxidation (IAAO)

- Human subjects fed different amounts of protein
- Indicator amino acid (typically $^{13}$C-phenylalanine) is fed
  - $^{13}$C comes out of the body as $^{13}$CO$_2$ when the amino acid is oxidized
- At low protein intakes, essential amino acid (EAA) intake is insufficient to support protein synthesis
  - Thus, IAAO is high
- As protein/EAA intake increases toward requirement, protein synthesis improves and IAAO falls
- At breakpoint, IAAO reaches lowest point and further increase in protein intake does not change it
  - The breakpoint is the estimated average requirement (EAR)
Basic principle of the IAAO method

IAAO studies to estimate human protein requirements

<table>
<thead>
<tr>
<th>Population (reference no.)</th>
<th>Mean age or age range, y</th>
<th>Proposed RDA/population safe intake (g/kg/d)</th>
<th>Current DRI RDA/AI (g/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (3)</td>
<td>6-11</td>
<td>1.55</td>
<td>0.95</td>
</tr>
<tr>
<td>Young adult males (4)</td>
<td>~27</td>
<td>1.20</td>
<td>0.80</td>
</tr>
<tr>
<td>Bodybuilders, male (1)</td>
<td>22.5</td>
<td>2.20</td>
<td>0.80</td>
</tr>
<tr>
<td>Endurance athletes, males (6)</td>
<td>28</td>
<td>1.83</td>
<td>0.80</td>
</tr>
<tr>
<td>Endurance-trained males, 24 h post-exercise (2)</td>
<td>26.6</td>
<td>2.60</td>
<td>0.80</td>
</tr>
<tr>
<td>Female athletes, variable intensity exercise (11)</td>
<td>21.2</td>
<td>1.71</td>
<td>0.80</td>
</tr>
<tr>
<td>Older males (8)</td>
<td>&gt;65</td>
<td>1.24</td>
<td>0.80</td>
</tr>
<tr>
<td>Older females (7)</td>
<td>&gt;65</td>
<td>1.29</td>
<td>0.80</td>
</tr>
<tr>
<td>Octogenarian females (10)</td>
<td>82</td>
<td>1.15</td>
<td>0.80</td>
</tr>
<tr>
<td>Pregnancy, 11-20 wk gestation (9)</td>
<td>24-37</td>
<td>1.66 (upper end, 95% CI from EAR)</td>
<td>1.10</td>
</tr>
<tr>
<td>Pregnancy, 31-38 wk gestation (9)</td>
<td>24-37</td>
<td>1.77 (upper end, 95% CI from EAR)</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval; DRI = Dietary Reference Intakes; RDA = Recommended Dietary Allowance; AI = Adequate Intake; EAR = Estimated Average Requirement
References from IAAO studies


Summary of IAAO studies

- In all the studies summarized in the table, each one had an EAR that was higher than the present RDA
  - The authors determined an EAR, then tacked on a couple of standard deviations to cover population requirements
- For non-exercising adults of all ages, the authors propose a protein RDA (1.15-1.30 g/kg/d) that is around 50% higher than the present RDA
- For athletes, the present RDA is 2-3 times too low
  - Intakes of 1.7-2.6 g/kg/d are recommended
Recommended protein intake and exercise from ESPEN expert group for older people

- For healthy older people, the diet should provide at least 1.0-1.2 g protein/kg body weight/day.
- For older people who are malnourished or at risk of malnutrition because they have acute or chronic disease, the diet should provide 1.2-1.5 g protein/kg body weight/day.
  - With even higher intake for individuals with severe illness or injury.
- Daily physical activity or exercise (resistance training, aerobic exercise) should be undertaken by all older people, for as long as possible.

ESPEN = European Society for Clinical Nutrition and Metabolism

Will the protein RDA change?

- Many experts in protein research have advocated for a higher protein RDA for the general population and specific sub-populations.
- Virtually all new evidence points to benefits of protein intakes higher than current RDA.
- No specific changes to the protein RDA are in the works, to my knowledge.
Protein: Not just amount, but also distribution counts

- Timing and distribution of protein intake is also important for promoting muscle protein synthesis.
- For non-exercisers, 0.3-0.4 g/kg/meal over 3-4 meals.
- For athletes, 0.4-0.55 g/kg/meal over at least 4 meals.
- Post-workout period is a good time to get one of those meals.

Making protein intake practical

- **Non-exercisers**
  - Shoot for 20-30 g protein 3-4 times per day

- **Exercisers**
  - Shoot for 30-40 g protein 4-6 times per day, with one of these meals being right after a workout

- **Rules of thumb**
  - Cup of milk or soy milk is around 8 g protein
  - Meat, poultry and fish contains around 7 g protein per ounce
  - Cheese is around 7 g protein per ounce
  - Protein shakes can be helpful, especially in postworkout period
## Protein Content of Various Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Protein Content, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 egg, 2 egg whites, or 1/4 cup egg substitute</td>
<td>6-7</td>
</tr>
<tr>
<td>1 cup of milk</td>
<td>8-10</td>
</tr>
<tr>
<td>¼ cup cottage cheese</td>
<td>7</td>
</tr>
<tr>
<td>1 cup of yogurt</td>
<td>8-13</td>
</tr>
<tr>
<td>1 oz. of chicken, fish, pork, or beef&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
</tr>
<tr>
<td>1 oz. of cheese (except cream cheese)</td>
<td>7</td>
</tr>
<tr>
<td>1 slice of bread or ½ bagel</td>
<td>3</td>
</tr>
<tr>
<td>1 cup of cereal</td>
<td>3-6</td>
</tr>
<tr>
<td>2 tablespoons peanut butter</td>
<td>7</td>
</tr>
<tr>
<td>1/2 to 2/3 cup of dried beans or lentils</td>
<td>8</td>
</tr>
<tr>
<td>1 cup miso</td>
<td>8</td>
</tr>
<tr>
<td>4 oz. raw, firm tofu</td>
<td>9</td>
</tr>
<tr>
<td>½ cup peas or corn</td>
<td>3</td>
</tr>
<tr>
<td>½ cup of non-starchy vegetables</td>
<td>2</td>
</tr>
<tr>
<td>8 oz. soy milk</td>
<td>5-6</td>
</tr>
<tr>
<td>Protein drinks and powders/serving</td>
<td>10-45</td>
</tr>
</tbody>
</table>

<sup>a3</sup>-ounce portion (21 g protein) is the size of a deck of cards.

Protein intakes of Americans
Protein intake: How are we doing?

Data from National Health and Nutrition Examination Survey (NHANES) 2011-2014

- Average protein intakes were ~1.2-1.3 and 1.1 g/kg ideal body weight/d for young adults (19-50 y) and those aged 71+ y, respectively.
- However, substantial numbers of people were below RDA (which may already be too low).

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>% below RDA, Female</th>
<th>% below RDA, Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-13</td>
<td>6.92</td>
<td>2.31</td>
</tr>
<tr>
<td>14-18</td>
<td>23.36</td>
<td>11.26</td>
</tr>
<tr>
<td>19-30</td>
<td>14.01</td>
<td>2.75</td>
</tr>
<tr>
<td>31-50</td>
<td>13.23</td>
<td>4.27</td>
</tr>
<tr>
<td>51-70</td>
<td>15.59</td>
<td>7.17</td>
</tr>
<tr>
<td>≥71</td>
<td>19.21</td>
<td>13.17</td>
</tr>
<tr>
<td>≥80</td>
<td>16.74</td>
<td>16.86</td>
</tr>
</tbody>
</table>

Protein intake: How are we doing?

- Those 51 and older: Data from NHANES 2005-2014
  - 31-50% did not meet the RDA for protein (based on actual, not ideal, body weight)
  - Those not meeting protein RDA had more functional limitations across all age groups

- What about athletes?
  - A sampling of Dutch elite athletes showed:
    - Male athlete intake was 1.5 g/kg/d regardless of type of sport (101-123 g/d)
    - Female athlete intake averaged 1.4 g/kg/d (86-95 g/d)
  - Athletes were on the lower end of pre-existing sports nutrition recommendations and well below the amount that IAAO studies suggest for athletes

Is there a benefit for older people to hit higher protein intake targets?

- 12-wk study in 120 South Korean adults (70-85 y)
- Subjects were classified as pre-frail or frail based on validated questionnaires
- Baseline dietary protein intake was 0.8 g/kg/d
- Subjects randomly assigned to 3 isocaloric protein intakes
  - 0.8 g/kg/d (N=40)
  - 1.2 g/kg/d (N=40)
  - 1.5 g/kg/g (N=40)
- Supplemental protein came from whey protein
- No exercise training component to the study

Results from Park et al. (2018)

- For the 1.5 vs. 0.8 g/kg/day protein intake groups:
  - Muscle mass in arms and legs more than doubled
  - Indices relating arm and leg muscle mass to body weight, BMI, and body fat all significantly improved
  - Gait speed significantly improved
  - Other markers of nutritional status or performance did not improve
  - No adverse health effects were observed
- The 1.2 g/kg/d group showed intermediate results that were not significantly different than 0.8 g/kg/d
Similar results from other studies

- Resistance-training older women in Brazil\(^1\)
  - Protein intake increased from \(~0.96\) to \(~1.4-1.5\) g/kg/d (from whey)
  - Greater increases in skeletal muscle mass, strength, and 10-m walk time
- Army recruits in 8 wks of entry training\(^2\)
  - 77 g/d of extra whey protein vs. carbohydrate placebo
  - Decreased body fat mass and improved push up performance (+7)
- Older men and women (~68 y) undergoing energy and activity restrictions\(^3\)
  - 60 g extra protein/d from whey or collagen (total protein intake of 1.6 g/kg/d)
  - Neither protein protected against muscle loss from energy or activity restriction
  - Only whey protein increased lean muscle mass during recovery from activity and energy restriction

How much protein is too much?
Can you get too much protein?

- Potential ways to think about this issue
  - Direct protein toxicity (effects on liver and kidneys)
  - Indirect protein toxicity
    - Effects on bone?
      - Buffering of acid load
      - Increased urinary calcium loss
  - Other undesirable nutrient changes that accompany some high protein foods
    - Red meat and colon cancer link
    - Saturated fat and heart disease risk
  - Effects of protein excess on other nutrients in the body
    - High protein intake may crowd out other nutrients
What does the Health and Medicine Division say about too much protein?

- For several nutrients they have established Tolerable Upper Intake Levels (UL)
  - UL = The highest average daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.
  - No reliable evidence of adverse effects could be identified upon which a UL for excessive protein intake (no UL established)
- Acceptable Macronutrient Distribution Range (AMDR) for adults
  - Carbohydrate: 45-65% of daily energy
  - Protein: 10-35% of daily energy
  - Fat: 20-35% of daily energy

“Rabbit starvation” and direct protein toxicity

- No, it’s not about starving old Bugs!!
- Arctic explorer Vilhjalmur Stefansson observed illness in those forced to live on large quantities of very lean meat (i.e., rabbit) alone
  - Symptoms can include nausea, vomiting, diarrhea, fatigue and it can be fatal
  - Experienced this himself in a lab when he went on all meat diets with varying protein:fat ratios
  - Symptoms abated with increase in fat intake
- Some of these explorers could have surpassed the maximal rate of urea formation
- Must be above 35% of daily energy from protein and have restricted fat or carbohydrate

Evidence that high protein intake is safe in a normal diet (no direct toxicity)

- Protein intakes of 2.51 to 3.32 g/kg/d for 1 year in 14 healthy, resistance-trained men\(^1\) caused no harmful effects on:
  - Liver function
  - Kidney function
  - Blood lipids
- Key consideration: people had healthy livers and kidneys to start with
- Other studies, with 3.4 and even up to 4.4 g/kg/d\(^2,3\), in resistance training individuals have shown:
  - No adverse effects on blood tests for liver or kidney safety
  - No adverse effects on body fatness

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Potential for indirect protein toxicity

- Direct protein toxicity is extremely unlikely
- What about indirect protein toxicity?
- One example is the “Acid Ash Hypothesis”
- Hypothesis:
  - Metabolism of protein and grain foods, with low potassium intake, produce mild chronic acid condition in the blood
  - Calcium and bicarbonate extracted from bone to buffer the acid load
  - Increased urinary loss of calcium
  - Decreased bone density due to loss of calcium
- Sounds good in theory, but is it true??
Several refutations of acid-ash hypothesis

- The hypothesis has been thoroughly refuted in 3 separate meta-analyses examining relationship between dietary acid load and bone mineral absorption.
- On high protein diets, the increased urinary calcium is typically associated with an increase in calcium absorption from the intestine.
- Effects at least cancel each other out.
- Meta-analyses of many studies have shown either positive or no adverse effects of high protein diets on bone health.
- Key factor, though, is that calcium intake must also be high.

The “Rebar” example: importance of protein for bone health

- Bone needs a structural framework (e.g., protein like collagen) and a mineral matrix (i.e., the calcium-containing compound hydroxyapatite) to deposit into that framework.
- It is a lot like the rebar and concrete you see in construction projects.
  - Protein is like the rebar: provides a framework and gives torsional strength.
  - Concrete is the mineral matrix: provides the structural rigidity.
- Need both for healthy bone!!!
What about increased colon cancer or heart disease risk?

- Red meat and colon cancer
  - Relationship is limited to some epidemiological studies
  - Is this potential issue really about the protein, or another attribute of the red meat (iron, choline, lack of fiber, other)?
  - What about a diet high in red meat AND high in fruits, vegetables and whole grains (e.g., athletes consuming a lot of calories each day)?

- Saturated fat and heart disease risk
  - Risk may be lessened by choosing leaner sources of protein
  - Again, issue is more about saturated fat than about protein per se

What about too much protein simply crowding out other healthy foods?

- This is my main concern for most people
- Many high protein foods are low in carbohydrate and low in dietary fiber
  - Eggs, beef, chicken, fish, poultry, hard cheese
- Conversely, many healthy high carbohydrate foods are low in protein
  - Fruits, non-leguminous vegetables, whole grain products
- Plant-based proteins, as part of your overall protein mix, are a great way to get protein as well as a lot of other beneficial nutrients
- The key is to not eat so many high protein foods that there is not enough intake of other healthy foods
Key take-homes regarding protein safety

- High protein diets within the AMDR of 10-35% of energy (and up to 2-3 times the RDA) pose no direct safety concern
  - Key proviso: that a person has healthy liver and kidney function to start
- High protein diets are unlikely to have an adverse effect on bone health and may have positive effects (remember your rebar)
- Indirect risks of high protein diets have less to do with the protein and more to do with other dietary factors that may do harm:
  - Perhaps too much red meat, saturated fat
  - Other healthy foods get crowded out with too much focus on protein
Overall summary and take home points

- Protein plays critical roles in many biological functions
- Consuming proteins from a variety of sources can help make sure we get all the essential amino acids that we need
- Current research suggests that protein recommendations such as the RDA may be too low to promote optimal health and function, especially as people get older
- Proper distribution of protein intake may be helpful as well
- Keeping protein intake within the AMDR (and up to 2-3 times the present RDA) appears to be safe
- Strike a balance between emphasizing enough protein and not crowding out other healthy foods from the diet
Questions?