Approach Used to Establish Adequate Intakes for Non-Essential Nutrients

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Nutrient Reference Values for Bioactives? New Approaches

2012 Scientific Symposium by CRN-International

December 1, 2012

Nutrient-based reference values are based on the relationships between nutrient intakes and indicators of adequacy, prevention of chronic disease, and avoidance of too high an intake of a nutrient

What Scientific Evidence is Needed?

- Epidemiological (observational)
- Randomized Clinical Trials (intervention)
- Animal/*In Vitro* Studies (mechanistic)

Association vs. Causality

Non-Essential Nutrients (Bioactives)

What are these?

- Include those oxidized as fuels and those that provide carbon skeletons and amino groups for endogenous synthesis of body constituents
- Cannot be made by the body and may be absorbed from foods consumed
- May have health benefits and may be considered part of healthy diet
- Not result in biochemical or clinical symptoms of deficiency

What are people consuming?

Dietary Assessment Methods

- Diet records (food diaries)
- 24-hour recall
- Diet histories
- Food frequency questionnaires
- Include supplement intake

Challenges

- All dependent on individual's ability to recall food consumed
- Estimate of whole food
- Estimate of food component
- Reliable food composition databases

Food Frequency Questionnaires

- Most commonly used
- Validated FFQs most reliable

Food Composition Databases

- Critical need: updated and reliable
- Sources of variability: food processing and cooking procedures, foods storage, seasonal variation, and nutrient/food component bioavailability
- USDA/ARS nutrient databases include: flavonoids (release 3, 2011), isoflavones (release 2, 2008), proanthocyanidins (2004)

Biomarkers

- Must be causally linked to outcome itself
- Biomarker of exposure
- Biomarker of effect
- Must be feasible, valid, reproducible, sensitive, and specific

Biomarker of Exposure

- Relates to a validated measure of nutrient intake
- Measure nutrient in the blood or balance studies used as indicator in setting DRI reference values
- Used to estimate inadequate and excessive intakes
- Measure substance itself or metabolite of substance

Biomarker of Exposure

- Issue: few reliable and validated biomarkers for most nutrients; same is true for non-essential nutrients
- Especially critical in estimating intake from observational studies
- Method of dietary assessment important

Clinical Studies

Human studies must:

- Measure the relative incidence of the onset of disease or measure validated, modifiable risk factors
- Biomarker of effect

Biomarker of Effect

- Intermediary endpoint
- Indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention
- Indicator that can be relied upon as causally related to and predictive of health outcome

Biomarker of Effect

- Most reliable: validate surrogate endpoints of disease risk
- Few of these

Diseases and Surrogate Endpoints of Disease Risk Recognized by FDA

- CHD – total/LDL cholesterol, blood pressure
- Colon/rectal cancer – polyps
- Diabetes – blood sugar levels, insulin resistance
- Osteoporosis – bone mineral density
- Dementia – mild cognitive impairment

Rely on NIH and FDA CDER

Biomarker of Effect

- Predict benefit or harm, modified by various factors, including diet
- Not all risk biomarkers are surrogate endpoints (e.g., c-reactive protein for CHD)
- May be in causal pathway, not accepted because lack scientific evidence to validate them (e.g., HDL cholesterol)

Validation of Risk Biomarker

- Analytical validation- analysis of available evidence on analytical performance of an assay
- Qualification- assessment of available evidence on associations between biomarker and disease states
- Utilization- contextual analysis based on specific use proposed and applicability of available evidence to their use

Challenges

- Limited validated modifiable risk biomarkers for chronic disease risk
- Not all risk biomarkers are surrogate endpoints
- Many chronic diseases lack surrogate endpoints

However….

- Scientific evidence includes studies in which risk biomarkers are not validated surrogate endpoints for chronic disease risk
- May be several pathways to disease
- Because of utility in filling data gaps, risk biomarkers are critical components in DRI process

Type of Studies

- Intervention studies- measure surrogate endpoint or incidence of onset of disease
- Observational studies- measurement of substance (food intake estimate, nutrient intake estimate is estimate of estimate); type of study- prospective, case-control, cross-sectional, etc. Considered less reliable, measure association
- Animal/*In Vitro* studies- possible mechanisms involved in relationship between food component(s) and disease

Prospective Studies

- Beneficial effects of fruit and vegetable consumption
- Which nutrients/non-nutrients responsible?
- Substitution effect?
- Disease risk multi-factorial

Example: Total Fiber

- Combination of dietary fiber and functional fiber
- Non-essential nutrients
- Established an AI, but not EAR
- Based on intake levels observed to prevent CHD. Data included observational, clinical, and mechanistic
- Reduction of risk for diabetes used as secondary endpoint to support recommended intake levels

Health Benefit Attributions

Fiber-rich foods have:

- Micronutrients and other biologically active compounds with distinct physiological and biochemical effects in humans contained in same foods
- Fiber that is released from plant cellular structure or that exerts its effect in GI tract only as digestible nutrients are hydrolyzed during digestion

Epidemiological Study Evidence

- Epidemiological data showed increased intake of high fiber foods and reduction of CHD
- Epidemiological data suggested that diets high in fiber-rich foods decreased risk for hypertension, a risk factor for CHD
- Fiber-containing foods, which are considered dietary fiber

Epidemiological Study Evidence

- Not possible to distinguish between effects of dietary fiber per se and fiber-rich foods
- Fiber-rich foods contain other compounds, such as phytochemicals, that could be responsible for reducing disease risk
- Foods high in fiber, usually low in fat, saturated fat, and cholesterol

Epidemiological Study Evidence

- Based primarily on 3 studies: Health Professionals Follow-Up Study, Nurse's Health Study, and Finnish Men Study
- Controlled for energy, saturated fat, alcohol, BMI, and various vitamins
- Strong relationship between cereal fibers and a weak or no relationship between vegetable and fruit fibers and CHD

Epidemiological Study Evidence

- Possible to relate number of grams of dietary fiber per day to reduced risk of CHD
- Indicators of dietary fiber intake used such as cereals, vegetables, fruits, whole grains or legumes

Intervention Study Evidence

- Experimental data showed blood cholesterol lowering effect of dietary fibers
- Human and animal studies showed certain types of fiber and lower levels of cholesterol

Intervention Study Evidence

- Strongest evidence in reducing blood lipid levels, thus reducing risk of CHD found in decreased total cholesterol and LDL cholesterol in studies using oat products or beans (dietary fiber) and functional fibers such as guar, pectin, and psyllium
- Not due to replacement of fat

Is it Fiber Per Se?

- Overall dietary pattern may be responsible for beneficial effect
- Isolating fiber as single factor is difficult and needs to be evaluated in context of total dietary pattern
- Some benefits associated with fiber may be due to other food components of fruits, vegetables, and cereal products
- Reported benefits may be due to fiber source, not necessarily fiber per se

Basis for AI

- Number of epidemiological studies showed individuals that consumed high amounts of dietary fiber and fiber-rich foods had reduced CHD risk
- Large prospective cohort studies showed significant inverse relationship between total fiber intake and risk of CHD, together with evidence from clinical and mechanistic data; an AI for total fiber was set

Basis for AI

- Some investigators analyzed diets for dietary fiber, others used indicators of dietary fiber intake such as cereals, vegetables, fruits, whole grains, or legumes
- Despite this, preponderance of data from epidemiological, intervention, and mechanistic studies were strong enough to set a recommended level of intake

Another Example: β-Carotene

and other carotenoids reviewed for potential DRI

- Epidemiological evidence suggested higher blood concentrations of β-carotene and other carotenoids from foods associated with lower risk of several chronic diseases
- Observed effects possibly due to other substances found in carotenoid-rich foods or to behaviors associated with increased intake of fruits and vegetables

β-Carotene

- Further evidence- 3 large RCTs indicated lack of evidence of overall benefit on total cancer or cardiovascular disease
- Possible harm from large doses in certain populations, such as smokers and asbestos workers

Conclusion

- Need to understand role of nutrient in a food matrix
- Difficult to base a DRI, e.g., AI strictly on dietary patterns
- Dietary patterns may indicate reduced risk for chronic disease, but…..

Conclusion

- Large, RCTs play critical role in establishing the relationship between intake of nutrients (essential/non-essential) and risk of chronic disease
- Need to establish strong scientific evidence for basing public health recommendations for healthy populations
- More claims exist for nutrient/disease relationships than are scientifically supported

What is the potential harm in making a public health recommendation on data based on large prospective cohort studies when there is a lack of large randomized controlled trials versus the potential harm of not making it?

THANK YOU

QUESTIONS???