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THE INSTITUTE OF MEDICINE'S RECOMMENDATIONS FOR VITAMIN D [1-1]

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

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HIGHLIGHTS AND EDITORIAL COMMENTS JANUARY 2011

IOM Recommendations for The General Healthy Population

1-1 THE INSTITUTE OF MEDICINE REPORTS ON VITAMIN D AND CALCIUM

[Note: This is not the official communication from the IOM. I abstracted it from the JAMA February 2, 2011;305:454-56 "Medical News and Perspective" by Anna Slomski, JAMA Staff Editor]

The governments of U.S. and Canada recently charged a group of scientists (The Institute of Medicine [IOM]) with updating the Dietary Reference Intake for vitamin D and calcium.

The committee reviewed 1000 studies on 25 health outcomes.

They also flatly declared that "the data just aren't there" to recommend that people consume *high* amounts of D and calcium.

Vitamin D:

They did recommend a higher D intake--a three-fold increase of some age groups--compared with levels set by the IOM in 1997:

- 1) Generally, to maintain bone health, 600 IU daily.
- 2) After age 70, 800 IU daily if the individual is not physically active and has significant declines in kidney function.

This new Recommended Daily Allowance (RDA) is a measure of nutrient intake that meets the needs of 97%% of the population. (In 1997, the recommendation was for 200 IU daily for persons up to age 50; 400 IU for those 51 to 79; and 600 IU over 70.)

The committee set the upper safe boundary to daily intake at 4000 IU of D. But this is not the amount people should aim for.

Although most North Americans get one third of their D requirement through skin synthesis, the committee took a "markedly cautious approach" in setting its new level for D based on sunlight exposure. Sunlight as a source of D is a problem because of the known risk of UV-induced skin cancers. But getting enough D from diet alone is problematic.

The claim that there is widespread D deficiency is based on the lack of consensus on how to define adequate serum levels of 25-OHD. The committee defined deficiency as below a level of 12 ng/mL, and insufficiency as 12 to 19 ng/mL.

The committee thinks that 20 ng/mL meets the needs of almost all of the healthy population, and found no evidence that going higher confers additional benefit. Other prestigious foundational and societies set the lower normal limit at 30.

The committee set the upper limit of D at 4000 IU/d so there is no downside to individuals increasing their intake to 1000 IU daily.

There is evidence that higher serum levels of D at or above 40 ng/mL are associated with all-cause mortality, pancreatic cancer and prostate cancer. Above 10 000 IU/d, there is clear evidence of risk.

But even assuming the 20 ng/mL is the threshold for adequate serum levels of D, a significant portion of the U.S. population remains insufficient. NHANES in 2000-2004 found that 50% of black children and teenagers had levels of 25-OHD less than 15 ng/mL, as did 9% of all children. Of the teens tested, 61% had D insufficiency at levels of 15 to 19. In one study, serum levels 76% pregnant women at term were insufficient, (serum D less than 20), as were 81% of infants.

The committee declared an “urgent need” to standardize D assays, and develop consensus for recommended values.

In the last few years, there has been a dramatic increase in testing serum D levels as part of routine medical care. Physicians should judge the risk for low D in each individual, and assess whether they need testing.

The new IOM recommendations are for the general healthy population and do not pertain to people with medical conditions that can cause malabsorption of D and calcium.

In evaluating the purported role of D in preventing numerous diseases, the IOM committee said that there is a paucity of randomized clinical trials. Observational studies provide conflicting evidence. This led to their conclusion that numerous links to outcomes, other than bone health, are best described as hypotheses of emerging interest.

Calcium:

The calcium requirement did not change appreciably. North Americans need from 700 to 1300 mg/d depending on age.

The committee set the safe upper boundary of daily calcium intake at 2000 to 3000 mg, but this is not the amount people should aim for.

Calcium from diet and supplements:

Most individuals can achieve the recommended amounts of calcium through diet alone. Some age 9 to 18 fall short of the recommended 1300 mg.

Many postmenopausal women are at risk of failing to consume the recommended 1200 mg through diet alone. But many who take calcium supplements are getting too much. “Many physicians have incorrectly interpreted women’s total 1200 as the amount they should be getting in a supplement.” Most

people get at least 600 mg and up to 900 mg from their diet and are also taking a 1200 mg supplement. They may be beyond the 2000 mg safe upper limit.

The committee found that 5% of women older than 51 had an intake above the upper limit, putting them at risk for kidney stones and possibly cardiovascular disease.

I believe we can depend on some points:

- 1. Many persons of all ages in the U.S. are D insufficient and require supplementation. This includes teens and pregnant women. Elderly persons, sedentary and living indoors in nursing homes, are especially prone to D insufficiency. Would it not be reasonable to treat them with 1000 IU of D daily on an empiric basis?*
- 2. Don't depend on sunlight to produce enough D.*
- 3. D supplements are safe up to 4000 IU daily. Do not aim for this amount.*
- 4. We still do not know the lower normal level of serum 25-OHD. It may be 20 ng/mL or 30 ng/mL*
- 5. Many teens fail to ingest the required calcium of 1300 mg daily--this at a time when bones are maturing.*
- 6. Some persons are taking too much calcium, some by over supplementation advised by their physician. Don't exceed 2000 mg daily.*
- 7. The data on preventing of diseases other than bone is based on observational studies and remain a hypothesis of emerging interest.*
- 8. For a normal healthy person:
For D: 600 IU daily; after age 70, 800 IU
For calcium: up to 1300 mg; no more than 2000 mg daily.*

Fortunately, the benefit / harm-cost ratio of supplemental D is very high. Some pharmacies sell 1000 IU of D3 for 3 cents each.

This abstract focused mainly on normal requirements of healthy people.

For those who are insufficient or deficient, higher doses are required.

See the following abstract

1-2 VITAMIN D INSUFFICIENCY

Serum 25-hydroxy vitamin D (**D**; **25-OHD**) deficiency, below 10 ng/mL (25 nmol/L), has long been recognized as a medical condition. It is characterized by muscle weakness, bone pain and fragility fractures. D is critical for skeletal mineralization.

Low dietary intake of D coupled with negligible exposure to sunlight may cause levels to decline below 10 ng/mL.

An international workshop (2007) agreed that most of the world's populations is not getting sufficient D to maintain healthy bone mass and to minimize risk of fracture. It also agreed that D insufficiency decreases muscle strength and increases risk of falls.

Vitamin D *insufficiency*, variously described as 25-OHD 10 to 29, or 10 to 19 ng/mL without overt clinical symptoms, has recently become a concern. The average dietary intake of D (including supplements) in the US is 200 IU per day. Skin-derived synthesis of D is quite variable,

Whatever range is used, the estimated prevalence of D insufficiency is as high as 50% to 80% in the general population.

A 2007 meta-analysis of 29 trials of supplementation with both calcium and D and with calcium-alone suggested that daily supplementation with 1200 mg calcium and 800 IU D reduced rates of fracture and modestly increased bone mineral density,

A 2009 Cochrane meta-analysis testing the effects of D supplements alone showed no significant reduction in risk of fractures. Combined calcium + D was marginally effective in reducing rate of fractures in the elderly as compared with no supplementation.

Observational studies have shown significant associations between levels of 25-OHD below 20 ng/mL and increased risk of metabolic, neoplastic, and immune disorders, multiple sclerosis, atherosclerosis, diabetes, and cardiovascular disease.

However, there is not enough data from large randomized trials to assess whether D supplements reduce risk of chronic disease other than osteoporosis.

Toxicity from D is rare. If it occurs, it is usually in the form of acute hypercalcemia, which usually result from doses that exceed 10 000 IU daily. Associated serum levels of 25-OHD are above 150 ng/mL. The Institute of Medicine (2009) set the tolerable upper level of D at 4000 IU daily.

In 2010 the International Osteoporosis Society, based on observational data, recommended a target serum level of 30 ng/mL in all elderly persons, and that a daily dose of 2000 IU may be necessary to attain that level.

In contrast, the Institute of Medicine suggested a 25-OHD level of 20 would protect 97.5% of the population against fractures and falls. The IOM recommended a dose of 600 IU daily for postmenopausal women who are not at high risk of fracture and falls, and 800 IU for persons who are over age 70.

How should primary care clinicians respond to these 2 articles? What should we believe?

Vitamin D (is it really a “vitamin”?) remains as the only vitamin deficiency which is wide-spread in developed countries. The average daily intake is low.

After all these years, there is much we still do not know. We can't agree on the biochemical definition of insufficiency. This should be settled. We can believe that insufficiency is common. We cannot rely on sunlight to produce the optimal amount. Supplements must be added. We cannot agree on the dose of supplementation. For bone health, calcium supplementation is also required. I believe, in general, modest doses (eg, 1000 mg daily) are sufficient.

Except for effects on bone metabolism, the benefits of supplementation are not known. We may be overtreating those with serum 25-OHD levels 20 to 30. But D at usual doses is non-toxic.

It is inexpensive .

I believe primary care clinicians should err on the side of advising supplements: 1000 and 1000 might be a good rule of thumb.

There are individuals for whom empiric supplementation is a reasonable approach--elderly persons living indoors; teen-agers, especially girls (they should enter menopause with a strong bone structure); and women entering the menopause, when loss of estrogen deficiency leads to rapid bone loss.

We do not necessarily have to await results of serum levels.

The dose of calcium should be modest-- not over 2 grams a day.

We await large long-term randomized controlled trials to determine if D has any effect on other disorders.

Even Small Amounts of Pre-Existing Albuminuria Should Be A Red Flag

1-3 PROTEINURIA AND RISK OF ACUTE KIDNEY INJURY

A study of nearly one million adults published in this issue of Lancet¹ showed an independent association between estimated glomerular filtration rate (eGFR), proteinuria and incidence of acute kidney injury. It provided evidence that the risks of progression to end-stage kidney disease and death associated with acute kidney injury vary with proteinuria as well as eGFR.

Patients with eGFR of 60 mL/min per 1.73 m² and proteinuria (urine dipstick trace to 1+; mainly albumen) have 2.5 times the risk of hospital admission with acute kidney injury as do those with no proteinuria. Risk increased to 4.4 times with heavy proteinuria (dipstick proteinuria > 2+).

This confirms and expands reports suggesting that both eGFR and proteinuria are potent risk factors for subsequent acute kidney injury.

The “Atherosclerosis Risk in Communities” a population-based cohort study (2010) reported that even high-normal albuminuria increased risk for subsequent hospital admission for acute kidney injury independently of known risk factors such as eGFR and comorbid conditions.

Acute kidney injury is a growing public health issue. Admissions to hospital are now nearly as common as admissions for stroke. Some cases of acute kidney injury might be iatrogenic and preventable. In patients who are critically ill, drug-induced nephrotoxicity accounts for nearly a fifth of cases of acute kidney injury.

Contrast-induced nephropathy is well described and potentially avoidable. Among hospital admissions with acute kidney injury the frequency of antecedent intravenous contrast has increased over the past decade. Many procedures involving contrast administration are elective. More accurate identification of high risk patients might allow timely implementation of preventive measures. Although serum creatinine is commonly checked before a contrast load, few think of a urine dipstick.

Preventing kidney injury is paramount because we have little treatment to offer.

Acute kidney injury should be recognized as a potent predictor for long-term morbidity and mortality. Even small amounts of pre-existing albuminuria should be a red flag when assessing kidney-risk profile.

Urinary dipstick is cheap, simple, and widely available. It might be a start to reversing the world-wide trends in acute kidney injury, a common and deadly disease.

Lancet, December 18/25, 2010; 376: 2046-47 “Comment” first author Morgan Grams, Johns Hopkins School of Medicine, Baltimore MD

1 Glomerular Filtration Rate, Proteinuria, and the Incidence and Consequences of Acute Kidney Injury
Lancet December 25, 2006-2103 (See full abstract)

I abstracted this article because detection of proteinuria by dipstick is simple, inexpensive, available, and almost instantaneous.

Detecting a decrease in kidney function (by both dipstick and eGFR) is important before subjecting a patient to drugs and procedures potentially harmful to the kidney. It may lead to substitution of a potential kidney-damaging drug by a less damaging drug.

Patients undergoing extensive surgical procedures (especially cardiac procedures) may develop impaired kidney function. If kidney function is impaired before surgery, the risk is magnified.

1-4 ANTIBIOTIC THERAPY FOR IRRITABLE BOWEL SYNDROME

The irritable bowel syndrome (IBS) is one of the most common conditions seen in primary care practice. Treatment is limited because of lack of understanding the pathophysiology of the syndrome, which is probably heterogeneous.

Alterations in the bacterial flora of the bowel are being considered a possible pathogenic factor.

Probiotics have been studied as treatment, but improvement is limited.

A study in this issue of NEJM¹ reports the results of 2 identically designed large double-blind placebo-controlled studies of rifaximin² in patients with IBS without constipation. Randomized over 1200 patients to 1) rifaximin three times daily. or 2) placebo for 2 weeks, followed by 10-week post-treatment observation.

The primary end-point was the proportion of patients who reported adequate relief of symptoms assessed by a questionnaire.

A key secondary end-point was adequate relief of bloating.

Rifaximin is a poorly absorbed broad spectrum antibiotic acting against gram positives and gram negatives, including *C difficile* and anaerobes It is extensively used for traveler's diarrhea. It has a favorable safety profile, low risk of side effects, and low risk of producing bacterial resistance.

In both studies, rifaximin vs placebo patients consistently met the criteria for relief of global IBS symptoms (41% vs 32% for placebo) and IBS-related bloating (40% vs 30%) for at least 2 of the first 4 weeks. Similar benefits were obtained for relief of IBS symptoms. during the 10-week post-treatment period, although benefits in both groups gradually decreased.

The advantages of the drug are the short treatment period, the sustained beneficial effects for 10 weeks, and the benefit on reducing bloating, which is one of the most challenging symptoms of IBS.

But the therapeutic gain of treatment in providing adequate relief ranged between 9% and 12 % compared with placebo. This is at the lower spectrum of what is considered clinically relevant. (NNT = 10)

IBS is a chronic disorder. Although benefit persisted after a 2-week treatment period, the response over time suggests some loss of efficacy toward the end of 10 weeks. It is not known if patients will benefit from a second course of therapy.

The mechanism of action is controversial. Initial studies of absorbed antibiotics were based on the hypothesis that these patients have small intestinal bacterial overgrowth. But later studies with jejunal aspiration and bacterial culturing did not support the theory. The most likely mode of action of rifaximin is a reduction in the overall bacterial load, especially in the large bowel. This may led to less bacterial

fermentation and less bloating, possibly combined with decreased secretion of bacterial products that contribute to the generation of symptoms.

At present rifaximin is not approved for the treatment of IBS. FDA approval is pending.

The drug has the potential to provide a welcome addition to the limited number of drugs that are available to treat IBS. It has a favorable safety profile. No treatment-associated cases of C difficile colitis have been reported.

Presently, clinicians should proceed with caution in using this drug. IBS is a chronic condition. The efficacy of rifaximin used repeatedly or chronically for treatment of IBS is not known. The risk of bacterial resistance may be high.

It may be reasonable to try one course for treatment of IBS in patients without constipation who have failed other treatments.

NEJM January 6, 2011; 364: 81-82 Editorial by Jan Tack, University of Leuven, Belgium

1. "Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation" NEJM

January 6, 2011; 364: 22-32 Original investigation, first author Mark Pimentil, Cedars-Siani Medical Center < Los Angeles.

At the end of the 2 weeks, active treatment provided benefit in 48% vs 41% in the placebo group. At the end of the trials (12 weeks) 34% vs 26%. [My assessment of figure 4 page 30]

The placebo response was high. Benefit of rifaximin remained higher than placebo over 12 weeks although benefits of both gradually decreased. The advantage of rifaximin remained. As noted, the NNT is at the borderline of clinical effectiveness.

2. Rifaximin (*Xifaxan*; Salix Pharmaceuticals) is a semi-synthetic rifamycin-based antibiotic. It is poorly absorbed (< 4%) In addition to treatment for traveler's diarrhea, it has been used to treat hepatic encephalopathy, for which it is approved by the FDA in 1998.

The company is seeking FDA approval for treatment of IBS, which requires 2 valid RCTs showing acceptable efficacy and safety.

Use now would be off-label. However, the drug has been used for years for other indications. It may be worth a try in a troubled patient, after fully informing her of benefits and risks, and allowing her to choose..

I do not know the cost of the drug.

1-5 WILL AN ASPIRIN A DAY KEEP CANCER AWAY?

Observational studies and randomized trials indicate that long-term aspirin use reduces incidence and mortality from colon cancer. Evidence of benefit from randomized trials for other cancers is limited.

A study in this issue of *Lancet*¹ provides important new evidence that long-term daily aspirin lowers mortality from several cancers other than colorectal cancer, and could have a meaningful effect on overall cancer mortality.

In eight randomized trials lasting up to 9 years, cancer mortality was 21% lower in the aspirin group than in the control group due mainly to a 34% reduction in colon cancer mortality.

In a longer-term analysis of 3 of the 8 trials, including 20 years of follow-up from the intervention and post-intervention periods, cancer mortality was 22% lower in those randomized to receive aspirin for 5 to 9 years than in controls.

The analysis of dose and duration of aspirin found that 75 to 100 mg daily seemed to be as effective as larger doses. However, even the lower doses of aspirin cause substantial risk of gi bleeding, possibly as much as 300 to 325 mg. No reduction in cancer mortality was noted in the first 5 years of aspirin use. Daily use for at least 5 years will probably be needed to reduce cancer mortality.

This contrasts with the results of the Woman's Health Study (2005), a large 10-year randomized trial of 100 mg aspirin taken every other day, which reported no benefit in overall cancer mortality. This might be explained by differences in the study population, by chance, or by the need to use aspirin daily to produce benefit.

What fatal cancers in addition to colon cancer might aspirin help to prevent? Benefits on esophageal, stomach, and lung cancer mortality seem likely. The reduction in esophageal cancer has been supported by observational studies. Reports of benefit on lung cancer have varied. Benefit was reported also in the Women's Health Study. Results for prostate and pancreatic cancers are suggestive, but should be interpreted with caution. Effects on prostate cancer mortality were not statistically significant. Pancreatic cancer mortality was significantly lower, but observational studies have not supported any effect.

Can we assume that, after 5 years of daily aspirin, an individual will experience a 34% reduction in the risk of fatal cancer as suggested by the intervention period analysis?

Assumptions about the exact magnitude of effects on cancer mortality should be made with caution. Confidence intervals indicate that the reduction in risk could plausibly be as low as 13%, and results for overall cancer mortality might not be completely generalisable to populations.

Clinical guidelines for aspirin use from the US Preventive Services Task Force recommend *not* using aspirin specifically for colorectal cancer prevention, and do not consider cancer when balancing the risk of serious gastrointestinal bleeding against the benefit from prevention of cardiovascular disease.

These investigators are justifiably enthusiastic about their work.

Investigators and journal editors persist in reporting benefits in terms of relative risk or hazard ratios. This can be very misleading. Patients maybe very impressed when told interventions X will reduce their chance of death by 33%. But less impressed when told they have less than one chance in 100 of benefiting.

However, they barely mentioned adverse effects of aspirin, although the trials were initially designed to prevent cardiovascular disease.

Primary prevention of CVD by aspirin has been discouraged because harm (mainly GI bleeding) outweighs benefits. Secondary prevention of CVD continues.

How should primary care clinicians respond to these findings?

At present, I believe harms will outweigh benefits. The NNT with long-term aspirin are very high, indeed, much higher than most clinicians would judge to apply to practice. I expect bleeding would outweigh benefit. Compliance with daily aspirin for years is problematic in primary care practice.

Perhaps some individuals who have a strong family history of GI cancer would be willing to risk possible harms of daily aspirin over 20 years.

1 Lancet January 2, 2011; 377: 31-41 "Effect Of Daily Aspirin On Long-Term Risk Of Death Due To Cancer" Original investigation, first author Peter M Rothwell, University of Oxford, UK

Confirming the Effectiveness of the Vaccine

1-6 HERPES ZOSTER VACCINE IN OLDER ADULTS AND THE RISK OF SUBSEQUENT HERPES ZOSTER DISEASE

The pain of HZ is often disabling and can last for months or even years. Approximately 1 million episodes of HZ occur in the US annually.

This randomized cohort study (2007-2009) compared 75 781 persons who were given HZ vaccine with 227 283 matched controls. All who received the vaccine were community dwelling and immunocompetent and age 60 and over.

This study evaluated the effectiveness of the vaccine under field conditions. (Ie, the effect when the vaccine is applied by primary care clinicians to the general population.).

| | Vaccinated | Not vaccinated |
|---------------------------------|---------------|-----------------|
| Follow-up (mean-years) | 1.72 y | 1.56 y |
| Overall incidence of HZ | 828 of 75 781 | 4606 of 227 283 |
| % | 1.09 | 2.03 |
| Absolute difference | 0.94% | |
| Incidence per 1000 person-years | 6.4 % | 13.0% |
| NNT | 106 | |
| Hazard ratios | | |
| HZ | 0.45 | 1.00 |
| Ophthalmic HZ | 0.37 | 1/00 |
| Hospitalizations for HZ | 0.24 | 1.00 |

Among unvaccinated persons incidence of HZ was more common in those over age 80, in women, and whites.

Overall, herpes zoster vaccine was associated with a 55% reduction in incidence of herpes zoster, which is consistent with the 51% vaccine efficacy reported from the original vaccine study. (2005)

The vaccine has the potential to prevent tens of thousands of cases of HZ and postherpetic neuralgia.

The Advisory Committee for Immunizations Practices recommends it for all healthy individuals over age 59.

Conclusion: Among immunocompetent community dwelling adults age 60 and older, the vaccine was associated with lower incidence of HZ Risk was reduced among all ages, and among individuals with chronic diseases.

HZ is a disease of waning immunity. It is growing as the present old generation grows older. For following generations, which have the advantage of receiving chicken pox vaccine in childhood and never experienced the disease, incidence of HZ may decrease markedly.

The HZ vaccine is good, but not perfect. Uptake by the public has lagged. I believe medical profession has failed to stress its importance.

I had forgotten how the terms were coined:

Herpes: herpein Gr. to crawl; Zoster: Gr. Belt or girdle

Shingles: L.: cingulus belt

ABSTRACTS JANUARY 2011

1-2 VITAMIN D INSUFFICIENCY

[Editor's note: "Vitamin D" (D) is a generic term. 7-dehydro cholesterol is the precursor of previtamin D in the skin, which is converted by ultraviolet radiation to circulating vitamin D3. D2 and D3 from the diet are added, and converted in the liver to 25-hydroxyvitamin D (25-OHD), which in turn is converted to 1,25-OHD in the kidney. 1,25-OHD has greater affinity for the D receptor, and is biologically more potent. However, 25-OHD, the chief circulating form, is easily measured in serum and is the form of vitamin D discussed in this article. Serum 25-OHD level is the best indicator of overall D status. It reflects total D from diet and sunlight. In this abstract "D" is used as a generic term, and sometimes synonymously with 25-OHD.

The clinical problem:

Serum 25-hydroxy vitamin D (**25-OHD**) deficiency (below 10 ng/mL--25 mmol/L) has long been recognized as a medical condition. It is characterized by muscle weakness, bone pain and fragility fractures. D is critical for skeletal mineralization. Numerous observations have linked low levels of D to fractures.

Vitamin D *insufficiency* (25-OHD 10 to 29 ng/mL), without overt clinical symptoms, has recently become a concern. Increased attention to this new "syndrome", and its potential complications, has led to a substantial increase in testing for serum 25-OHD. Laboratory assays for 25-OHD increased by several million in 2009.

The implications of 25-OHD levels below the normal reference range (below 30 ng/mL), but not markedly reduced, and the value of supplementation are incompletely understood. In the past several years, attention has turned to non-skeletal effects of D insufficiency, particularly in relation to cardiovascular disease, diabetes, cancer, and immune dysfunction.

This review summarizes the current understanding and uncertainties regarding D insufficiency and the effects of supplementation on health outcomes.

Strategies and evidence:

Defining D "insufficiency": Interpreting 25-OHD serum levels between 10 and 30 ng/mL is challenging:

- 1) Most reference laboratories have raised the lower boundary of the normal range to 30 ng/mL.
- 2) There are several ways to measure 25-OHD. Their precision and accuracy, especially in non-

reference laboratories, remains problematic.

3) 25-OHD levels change with the seasons, exposure to sunlight, and dietary intake. In northern latitudes, levels decrease by 20% from late summer to midwinter.

The average dietary intake of D (including supplements) in the US is 200 IU per day. Skin-derived synthesis of D is quite variable, depending on pigmentation, season, clothing, age, sunscreen use, and local weather conditions. Levels of 25-OHD are lower among blacks than among whites. In healthy whites, serum levels of 25-OHD vary according to environment and nutritional factors. The body mass index (**BMI**) is inversely related to the serum 25-OHD. Obese persons typically have levels in the range of 10 to 20 ng/mL. This may be due to less sunlight exposure.

Low dietary intake of D coupled with negligible exposure to sunlight may cause levels to decline below 10 ng/mL. Disease causing intestinal malabsorption can be associated with low levels. Use of phenobarbital and corticosteroids are associated with low levels.

With recent changes in laboratory reference ranges, a normal level is typically defined as between 30 and 76 ng/mL. When this range is used, the estimated prevalence of D insufficiency is as high as 50% to 80% in the general population. According to NHANES (2007) the mean 25-OHD level among several age groups was 24 ng/mL, a level associated with insufficiency according to some standards.

There are 2 rationales for setting the lower limit of normal at 30 ng/mL:

- 1) Parathyroid (**PTH**) levels rise when levels fall below 30.
- 2) Active calcium absorption is optimal when the level is 30.

However, both tenets are being questioned. Data indicate that there is substantial variation in the relationship between PTH and 25-OHD when levels are between 20 and 30. There is no absolute threshold level at which PTH rises. And there are too few studies to establish an absolute cutoff when calcium absorption is not enhanced. Generally speaking, peak absorption of calcium occurs at levels between 20 and 30.

Vitamin D and bone health:

D is critical for bone mineralization. Most D studies have assessed effect of D on outcomes of skeletal health.

A recent report from Ottawa on 15 studies concluded that associations between D and fractures, falls and performance measures (gait, stability, and activity) across elderly men and women are *not* consistent. A second study, analyzing the same studies, concluded that there was fair evidence of an association between low serum D and an increased risk of falls among institutionalized elderly people.

A 2007 meta-analysis of 29 trials of supplementation with both calcium and D and with calcium-alone suggested that daily supplementation with 1200 mg calcium and 800 IU D reduced rates of fracture and modestly increased bone mineral density,

A 2009 Cochrane meta-analysis testing the effects of D supplements alone showed no significant reduction in risk of fractures. Combined calcium + D was marginally effective in reducing rate of fractures in the elderly as compared with no supplementation.

Evidence between serum levels of 25-OHD and the risk of falls in the elderly is inconsistent. Randomized trials of supplementation with D2 or D3 (400 to 800 IU daily) failed to show significant effects on risk of fracture and falls in older persons. A longitudinal study of older men with serum levels below 20 ng/mL reported a higher risk of hip fracture than men with higher levels. However, another study of women reported the levels below 20 were not associated with increased risk of fractures over 5 years follow-up.

Vitamin D and other health effects.:

Observational studies have shown significant associations between levels of 25-OHD below 20 ng/mL and increased risk of metabolic, neoplastic, and immune disorders such as type 1 diabetes and multiple sclerosis. The two conditions most commonly associated with low levels are atherosclerosis and diabetes. A significantly increased risk of diabetes has been reported in individuals in whom D is insufficient (below 30), even after adjustment for BMI and percent of body fat. A prospective study reported that levels below 20 were associated with increased risk of cardiovascular disease.

However, there is not enough data from large randomized trials to assess whether D supplements reduce risk of chronic disease other than osteoporosis.

Despite the recent focus in the media on the potential role of D in reducing risk of various chronic diseases, this hypothesis requires large randomized controlled trials. D cannot currently be recommended for the purpose of reducing risk of cancer and heart disease.

Areas of uncertainty:

Optimal dosage for D remains uncertain. In general, for every 100 IU taken daily there is an increase of roughly 1 ng/mL in serum 25-OHJD. Data are scarce on the effects of long-term supplementation greater than 1000 IU per day. A recent randomized trial reported that elderly persons receiving 500 000 IU once a year for 3 years had an *increased* risk of falls and fractures compared with placebo. This suggests that high intermittent doses may be metabolized differently.

Data are lacking from large randomized, controlled trials (RCT) designed to determine whether D supplements reduce the risk of major diseases such as colon cancer, for which there are observational studies suggesting a reduction in risk. A 5-year RCT involving 20 000 US men and women receiving 2000 IU daily is ongoing to determine if D is associated with reduced risk of cancer and cardiovascular disease.

Toxicity from d is rare. When it occurs it is usually in the form of acute hypercalcemia, which results from doses that exceed 10 000 IU daily. Associated serum levels of 25-OHD are above 150 ng/ml. The Institute of Medicine (2009) set the tolerable upper level of daily intake of D at 4000 IU daily. The long-term effect of doses above 4000 IU is not known. Risks cannot be ruled out. Recent observations have suggested an association between serum levels above 60 ng/mL and pancreatic cancer, vascular calcification, and death from any cause. Cause and effect cannot be established by observations studies.

The optimal replacement dose in the elderly is not known.

Guideline from professional societies:

An international workshop (2007) agreed that most of the world's population is not getting sufficient D to maintain healthy bone mass and to minimize risk of fracture. It also agreed that D insufficiency decreases muscle strength and increases risk of falls. They recommended, on the basis of observational studies, that the minimal desirable level of serum 25-OHD is 20 ng/mL. In 2010, an osteoporosis group stated that the level should be at least 30 ng/ml, and that insufficiency should be defined as a level between 10 and 29.

In 2010 the International Osteoporosis Society, based on observational data, recommended a target level of 30 in all elderly persons, and that a daily dose of 2000 IU may be necessary to attain that level.

In contrast, the Institute of Medicine suggested a 25-OHD level of 20 would protect 97.5% of the population against fractures and falls. The IOM recommended a dose of 600 IU daily for postmenopausal women who are not at high risk of fracture and falls, and 800 IU for persons who are over age 70.

NEJM January 20, 2011; 364: 248-54 "Clinical practice" commentary by Clifford J Rosen, from the Maine Center Research Institute Scarborough Maine.

1-3 GLOMERULAR FILTRATION RATE, PROTEINURIA, AND THE INCIDENCE AND CONSEQUENCES OF ACUTE KIDNEY INJURY

Low estimated glomerular filtration rate (**eGFR**) predisposes to acute kidney injury. Proteinuria is a marker of kidney disease.

This study assessed how eGFR and proteinuria jointly modify the risk of acute kidney injury and subsequent adverse clinical outcomes.

STUDY

1. This cohort study followed 920 985 adults residing in Canada between 2002-2007.
2. Included patients with at least one outpatient measurement of both serum creatinine and proteinuria by dipstick (or albumin/creatinine ratio).
3. Determined hospital admissions for acute kidney injury over the follow-up period.
4. Also determined all-causes mortality and a composite of end-stage renal disease and doubling of serum creatinine.

RESULTS

1. During the median follow-up of 35 months, 6520 individuals (0.7%) were admitted to the hospital for acute kidney injury. (**AKI**)
2. For those with a eGFR 60 mL/min per 1.73 m² or greater, the adjusted risk of admission for AKI was about 4 times higher in those with heavy dipstick proteinuria vs no proteinuria.
3. The adjusted rates of admission with AKI and kidney injury requiring hemodialysis remained high in patients with heavy dipstick proteinuria for all values of eGFR.
4. The adjusted rates of death and the composite renal outcomes were also high in individuals admitted with AKI.
5. Rates of mortality and end-stage renal disease (**ESRD**) or doubling of serum creatinine in patients with and without acute kidney injury by baseline kidney function and proteinuria--per 1000 patient-years:

| Proteinuria | All-cause mortality | | | ESRD or doubling of creatinine | | |
|------------------|---------------------|------|-------|--------------------------------|------|-------|
| | None | Mild | Heavy | None | Mild | Heavy |
| eGFR 60 and over | 0.9 | 2.2 | 3.0 | 0.1 | 0.3 | 1.4 |
| eGFR 45 to 59.9 | 0.9 | 2.0 | 2.9 | 0.2 | 0.5 | 2.9 |
| eGFR 30 to 44.9 | 1.3 | 2.5 | 3.1 | 0.5 | 1.5 | 5.7 |

eGFR 15.0 to 29.9 2.3 4.1 5.4 2.0 6.0 28.0

(Note that, even if eGFR decreased markedly, and the patient had no proteinuria, risk of mortality and ESRD increased relatively little. As eGFR decreased and proteinuria increased, risks increased. Ed.)

CONCLUSION

Information on proteinuria and eGFR should be used together when identifying people at risk of acute kidney injury

Lancet December 25, 2096-2103 Original investigation, first author Mathew T James, University of Calgary, Alberta, Canada.

Daily Aspirin Reduces Death Due To Several Common Cancers. But, “more work is needed”

1-5 EFFECT OF DAILY ASPIRIN ON LONG-TERM RISK OF DEATH DUE TO CANCER

In the developed world, the lifetime risk of cancer is about 40%.

Treatment with daily aspirin for 5 years reduces risk of colorectal cancer. Several lines of evidence suggest that aspirin also reduces risk of other cancers, particularly cancers of the gi tract. Proof is lacking.

In contrast with treatment of cancer, there has been little progress in the use of drugs to prevent the disease.

This study used individual patient data from all randomized trials of daily aspirin vs no aspirin with a mean duration of 4 years or longer to determine the effect of allocation to aspirin on risk of cancer death.

STUDY

1. Used individual patient data from all randomized trials of use of daily aspirin (any dose) vs no aspirin with duration of treatment 4 years or longer. The original purpose of the trials was to determine effects on cardiovascular disease--both primary and secondary prevention.
2. Determined the effect of allocation to aspirin on risk of cancer death in relation to the scheduled duration of treatment.
3. Determined effect on risk of gastrointestinal cancers and non-gi cancers.
4. In 3 of 8 trials, long-term follow-up of individual patients was obtained to determine cancer deaths over a period of 20 years.

5. The effects of allocation to aspirin on risk of death due to cancer and all-cause mortality during each trial were expressed as odds ratios.
6. All analyses were by intention-to-treat.

RESULTS

1. In all 8 trials (25 570 patients; 674 cancer deaths) allocation to aspirin was associated with reduced cancer deaths.
2. Meta-analysis of the effect of aspirin on death due to cancer during all eligible randomized trials (n = 8) of aspirin vs no aspirin. (Figure 1, p 32)

| Aspirin | No aspirin | Odds ratio | % reduction |
|-----------|------------|------------|-------------|
| 327/14035 | 347/11636 | 0.79 | 21% |

(By my calculation, 2.3% of aspirin patients and 3.0% of no-aspirin patients died of cancer.

The difference = 0.7%. Ie, a reduction of 7 in 1000. (NNT to prevent one death by taking aspirin long-term= 141. Ed.)

3. Overall, benefit was evident only after 5 years of aspirin treatment. For stomach and colorectal cancer, benefit was not significant until after 10 years; for pancreatic cancer, 20 years.
4. Results after 5 years. Deaths from cancer aspirin vs no aspirin

| | Hazard ratio | % reduction |
|-------------|--------------|-------------|
| All cancers | 0.66 | 34% |
| Gi cancers | 0.46 | 54 |

5. Twenty-year risk of cancer death (163 cancer deaths; 12 639 patients)

| | | |
|-------------------|------|----|
| All solid cancers | 0.80 | 20 |
| Gi cancers | 0.65 | 35 |

6. Benefit increased as scheduled duration of trial treatment increased over 7.5 years.
7. Benefit was not related to aspirin dose (75 mg and up), sex, or smoking. Benefit increased with age. The absolute reduction in 20 -year risk of cancer death reached 7.08% at age 65 and older. (NNT = 14)
8. There was no effect on hematological cancers.
9. Overall, the absolute risk of deaths due to non-gastrointestinal cancers was 1.88% at 20 years. (NNT = 53).
10. Across all cancers, aspirin reduced only deaths due to histologically proven adenocarcinoma or primary carcinomas in which adenocarcinoma predominates.

DISCUSSION

1. “We showed previously that treatment with aspirin for longer than 5 years reduced the long-term risk of colorectal cancer. In analysis of nearly 2000 cancer deaths, we now show that aspirin also reduces death due to other common cancers.”
2. Aspirin reduced the risk of death due to cancer by about 20% during the treatment period.
3. The benefit was due mainly to delayed reduction of about 30% to 40% of deaths after 5 years of aspirin .
4. In long-term follow-up of 3 large trials, the reduction in death due to solid cancers was maintained at 20 years.
5. These effects were consistent across trials despite very different populations, suggesting that the findings are generalisable.
6. The benefit of aspirin increases with the duration of scheduled treatment.
7. The benefit was limited to certain cancers, more particularly adenocarcinoma.
8. The effect did not appear to increase as dose of aspirin was increased over 75 mg daily.
9. The absolute reduction in cancer deaths increased with age of the patient.
10. The effect of aspirin on risk of fatal cancers resulted in a small reduction in all-cause mortality.
11. This is the first proof that aspirin reduces death due to several common cancers. “More work is required.”

CONCLUSION

Daily aspirin reduces death due to several common cancers. Benefits increased with duration of treatment, and was constant across different study populations. “These findings have implications for guidelines for use of aspirin and for understanding carcinogenesis and its susceptibility to drug intervention.”

Lancet January 2, 2011; 377: 31-41 Original investigation, first author Peter M Rothwell, University of Oxford, UK

Confirming the Effectiveness of the Vaccine

1-6 HERPES ZOSTER VACCINE IN OLDER ADULTS AND THE RISK OF SUBSEQUENT HERPES ZOSTER DISEASE

The pain of HZ is often disabling and can last for months or even years. Approximately 1 million episodes of HZ occur in the US annually.

The Shingles Prevention Study (SPS; 2005)¹ is a clinical trial of live, attenuate vaccine prepared from the Oka-Merck strain of varicella zoster virus. (*Zostavax*; Merck). The trial included 38 546 participants 60 years old and older, who had no history of HZ. The vaccine reduced the incidence of HZ by 51% and postherpetic neuralgia by 67%. The FDA licensed the vaccine in 2006. The Advisory Committee for Immunizations Practices recommends it for all healthy individuals over age 59.

This study evaluated the effectiveness of the vaccine under field conditions. (Ie, the effect when the vaccine is applied by primary care clinicians to the general population.).

STUDY

1. This randomized cohort study (2007-2009) compared 75 781 persons who were given HZ vaccine with 227 283 matched controls. All who received the vaccine were community dwelling and immunocompetent and age 60 and over.
2. Most subjects **were** between ages 60 and 74.
3. Main outcome = incidence of HZ.

RESULTS

| 1. | Vaccinated | Not vaccinated |
|---------------------------------|---------------|-----------------|
| Follow-up (mean; years) | 1.72 y | 1.56 y |
| Overall incidence of HZ | 828 of 75 781 | 4606 of 227 283 |
| % | 1.09 | 2.03 |
| Absolute difference | 0.94% | |
| Incidence per 1000 person-years | 6.4 % | 13.0% |
| NNT** | 106 | |
| Hazard ratio | | |
| (HZ fully adjusted*) | 0.45 | 1.00 |
| Ophthalmic HZ | 0.37 | 1/00 |
| Hospitalizations for HZ | 0.24 | 1.00 |

(* Adjusted for anyone receiving prescriptions of corticosteroids, in any form.)

(** Number Needed to Treat to prevent one case HZ over 1.72 years after vaccination.)

2. Among unvaccinated persons incidence of HZ was more common in those over age 80, in women, and whites, in those with lung disease and in those who made more visits as outpatients (indication of health care-seeking)

DISCUSSION

1. “Our data complement the results of the original clinical trial (SPS) of herpes zoster vaccine, indicated that the vaccine was associated with reduced risk of herpes zoster in a community setting with its mixed population and routine clinical practices. Overall, we found that herpes zoster vaccine was associated with a 55% reduction in incidence of herpes zoster, which is consistent with the 51% vaccine efficacy reported from the SPS”.
2. The vaccine was associated with a reduced rate of ophthalmic HZ and hospitalizations attributed to HZ.
3. The results suggest that the benefits extend to persons of all ages for whom the vaccine is recommended. “Our results support recommendations to offer herpes zoster vaccine to eligible patients of all ages including the oldest population.” The oldest population is the most vulnerable to the disease. (*It may never be too late.*)
4. The benefit of the vaccine in preventing ophthalmic HZ is especially important.
5. The vaccine should be offered to all ethnic groups, and to many patients with chronic diseases, which might have interfered with functional immunity.
6. In the SPS, the vaccine was associated with less pain among individuals in whom HZ developed, and reduced the incidence of postherpetic neuralgia by 66%. The present study was not designed to determine this.
7. The vaccine has the potential to prevent tens of thousands of cases of HZ and postherpetic neuralgia.
8. Individuals age 60 and over who received HZ vaccine had a reduced risk of HZ regardless of age, race, and presence of chronic disease.
9. The durability of protection from the vaccine is not known.

CONCLUSION

Among immunocompetent community dwelling adults age 60 and older, the vaccine was associated with lower incidence of HZ. Risk was reduced among all ages, and among individuals with chronic diseases.

JAMA January 12, 2011; 305: 150-166 Original investigation, first author Hung Fu Tseng, Southern California Kaiser Permanente Pasadena CA

1 For an abstract of the Shingles Prevention Study go to www.practicalpointers.org June 2005