

PRACTICAL POINTERS
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VITAMIN D—NO ORDINARY VITAMIN

LIMITING SALT INTAKE TO REDUCE THE BURDEN OF CARDIOVASCULAR DISEASE

TWO NEW INCRETINS FOR TREATMENT OF TYPE 2 DIABETES—SAFETY AND EFFICACY

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LOW HEALTH LITERACY—A RISK FACTOR FOR DEATH IN THE ELDERLY

RISK OF CANCER FROM RADIATION, ESPECIALLY CT CORONARY ANGIOGRAPHY

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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 20-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.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

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Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS JULY 2007

Vitamin D Is No Ordinary Vitamin

7-1 VITAMIN D DEFICIENCY

“Once foods were fortified with vitamin D and rickets appeared to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved.”

Not so. Rickets can be considered the tip of the vitamin D-deficiency iceberg. Vitamin D deficiency remains exceedingly common in children and adults. In utero, deficiency can cause growth retardation and skeletal deformities. In adulthood, deficiency can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscular weakness, and increase risk of falls and fracture. An estimated one billion people worldwide have vitamin D deficiency or insufficiency. More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels (< 30 ng per milliliter of 25-hydroxyvitamin D).

A meta-analysis evaluating the risk of fracture in older persons given 400 IU of vitamin D3 daily revealed little benefit in risk of fracture. In studies using 700 to 800 IU vitamin D3, hip fracture was reduced by 26% as compared with calcium supplements or placebo.

Most tissues and cells have vitamin D receptors. This has provided new insights into the multiple functions of the vitamin. The metabolism of vitamin D is complex, involving the gut, liver, kidney, bone, muscle, parathyroids, as well as the skin.

Vitamin D deficiency has been linked to many conditions other than bone and parathyroid metabolism. Directly or indirectly, 1,25 di-hydroxyvitamin D controls more than 200 genes. Lower serum levels have been related to increased incidence of colon cancer and breast cancer, multiple sclerosis, rheumatoid arthritis, and osteoarthritis as well as hypertension and cardiovascular disease.

The Institute of Medicine recommends 400 IU for adults age 61-70 and 600 IU for those over 70. Most experts agree that without adequate sun exposure, the requirements are 800 to 1000 IU daily. (*The author did not state whether D2 or D3. I presume D3. RTJ*)

“Much evidence suggests that the recommended ‘adequate’ intakes are actually inadequate, and need to be increased to at least 800 IU of D3 daily. It is very difficult to obtain that much D3 on a daily basis from dietary sources.”

Vitamin D2 is about 30% as effective as vitamin D3 in maintaining serum 25-hydroxyvitamin D levels; up to 3 times as much D2 as D3 may be required to maintain sufficient serum levels.

I belong to the “cod liver oil” generation when the mode was to give all children a teaspoonful daily—in retrospect, admirable.

I believe these special aspects of vitamin D warrant a long and detailed abstract. The time I spent on it was well worth while.

The main message is that, in our society, vitamin D status is almost universally deficient, and requires lifetime supplementation .Vitamin D is a safe drug.

The outreach of actions of vitamin D cited by the author will require much more observation to be confirmed as valid clinically.

Any disease as prevalent as osteoporosis in elderly persons should be prevented if possible. I believe it is possible to prevent or delay osteoporosis by the simple measure of continuing supplementation with vitamin D and calcium over a lifetime. (Universal prevention)

It is important to distinguish between D2 and D3. D3 is much more potent. D3 should be the form of choice.

A Vitally Important Public Health Issue

7-2 REDUCING THE POPULATION BURDEN OF CARDIOVASCULAR DISEASE BY REDUCING SODIUM INTAKE A Report of the Council on Science and Public Health of the AMA

The risk of developing hypertension derives from the effects of many factors in heredity and environment. Salt intake is an important component.

This review evaluates the scientific underpinning for reducing salt intake to decrease the public health burden of hypertension.

With few exceptions, observational studies examining various non-industrialized societies have correlated salt intake with the increased incidence of hypertension, or showed that, when salt was introduced into the diet, the prevalence of hypertension increased. Primitive societies with habitually low salt intake are normotensive and do not exhibit increases in BP with age. When they migrate, and adopt more modern lifestyles and increase salt intake, BP levels increase.

About 100 randomized controlled trials examining the effect of reducing salt intake on BP in normotensive and hypertensive individuals found that reducing salt intake lowered BP. Meta-analysis of 11 RCTs of patients at about or over age 60 concluded that a long-term high salt diet increased mean BP by 6/4 mm Hg.

The DASH-sodium trial of diets (fruits, vegetables, low fat, more potassium, fiber, and protein) combined with varying degrees of salt intake reported that the degree of salt restriction was related to greater BP reductions:

In the US, the average daily intake of salt in adults is now estimated to be about 10 grams per 2000 kcal. Between 1970 and today, salt intake has increased by 55%. (As the obesity epidemic flourished in America, the increased caloric intake was associated with increased salt intake.)

Practical Pointers has abstracted several other articles relating hypertension and CVD to salt intake.

I believe the subject bears repeating. See the May 2007 issue [5-1] "Sodium and Potassium in the Pathogenesis of Hypertension"

When I was abstracting the article, I thought of the remarkable change in population consumption of trans fatty acids that has occurred in the past few decades. After the scientific evidence of harm from trans fats became firmly established, the public quickly became aware of the risks. Governments and the food industry responded, and now trans fat contents appear on food labels. Some jurisdictions (New York City) have banned restaurants

from using trans fats. This public education program resulted in a public health benefit. Enjoyment of foods remained as before. There was no decrease in acceptance and enjoyment of foods.

I hope, and believe, the same will now occur with salt.

As the article states, this will rely on educating the public to request low sodium foods. And to be willing and able to recognize content of sodium and other nutrients on the “Nutrition Facts” labels of foods.

Natural foods contain little sodium. Almost all sodium intake in foods is in the form of salt (NaCl) added in food processing. Restriction of salt intake is the only effective means we have of lowering sodium intake in the diet.

Continued Evaluation In Clinical Practice Is Required To Determine The Role Of This New Class Of Drugs

7-3 EFFICACY AND SAFETY OF INCRETIN THERAPY IN TYPE 2 DIABETES: A Systematic Review and Meta-analysis

Efficacy of available therapies for type 2 diabetes mellitus (**DM-2**), even when used appropriately, diminishes as the disease progresses because of a steady, relentless decline in pancreatic beta-cell function. Current therapies are often limited by adverse effects such as weight gain, edema, and hypoglycemia. Most do not target postprandial hyperglycemia effectively. “Therapies targeting the decline in beta-cell function without causing weight gain and with minimal adverse effects are desirable.”

The improved understanding of the incretin effect on the pathophysiology of DM-2 has led to development of new hypoglycemic agents.

Incretins are peptides normally secreted by the intestine, released in response to glucose nutrients in the gut.

Incretins are composed primarily of 2 peptides which lower blood glucose levels:

- 1) An insulinotropic polypeptide increases insulin production and release from the pancreas.
- 2) A glucagon-like peptide impairs the normal action of glucagon and inhibits release of glucose from the liver.

These new drugs are moderately effective in improving glycemia. (HbA1c levels are lowered by ~ 1%) They have neutral or favorable effects on weight. They are safe and not associated with any serious adverse effects thus far. However, long-term safety and efficacy are not known.

Conclusion: Incretin therapy offers an alternative to currently available hypoglycemic agents in non-pregnant adults with type 2 diabetes. Efficacy is modest. Effects of weight are favorable.

Careful postmarketing surveillance for adverse effects and continued evaluation in clinical practice are required to determine the role of this new class of drugs for treatment of DM-2.

As a primary care clinician, I would not prescribe these drugs at present. I would wait several years for clarity of effectiveness and safety, and for costs to come down. In patients considered inadequately controlled (as measured by HbA1c levels), we already have effective and less expensive drugs to improve control (including

insulin). Note, there was no advantage of the incretin exenatide (Byetta) compared with insulin in non-inferiority trials.

If, as further observations become available, these drugs do indeed preserve beta-cell function, and the advantages on weight and a lesser risk of hypoglycemia become more evident, primary care clinicians may consider the benefit / harm- cost ratio to be favorable enough to prescribe them.

Merck is now promoting a combination of Januvia + metformin.

Completely New; Few Adverse Effects

7-4 PHARMACOLOGY OF BYETTA AND JANUVIA Incretin Mimetic And Incretin Enhancer: A Review

This review of the newly approved incretin mimetic and incretin enhancer for treatment of type-2 diabetes is included because they are an entirely new approach to therapy of DM2, may be an important clinical advance, and patients will be asking about them.

Primary care clinicians should be familiar with their pharmacology.

Read the full abstract.

Tricyclic Antidepressants Still First Choice

7-5 EFFECTS OF TREATMENTS FOR SYMPTOMS OF PAINFUL DIABETIC NEUROPATHY: A Systematic Review

The authors offer a treatment algorithm based on effectiveness and adverse effects. In order:

- A. Tricyclic antidepressants (Some patients may wish to try capsaicin first)
- B. Traditional anticonvulsants (sodium valproate; carbamazepine)
- C. Newer anticonvulsants (pregabalin; gabapentin)
- D. Duloxetine
- E. Opioid

See the full abstract.

I wonder—would the same algorithm apply to trigeminal neuralgia and post-herpetic neuralgia?

Is Atherosclerosis, At Least In Part, A “Postprandial Phenomenon”?

7-6 FASTING COMPARED WITH NON-FASTING TRIGLYCERIDES AND RISK OF CARDIOVASCULAR EVENTS IN WOMEN

Postprandial lipids may play an important role in the pathogenesis of cardiovascular disease. Postprandial TG-rich remnant lipoproteins can penetrate the endothelial cell layer, and reside in the subendothelial space, where they can contribute to the formation of foam cells, a hallmark of early atherosclerosis.

Elevated postprandial levels of TG also might represent an abnormal response to an oral fat load that reflects insulin resistance, a condition associated with a host of metabolic abnormalities that predispose an individual to cardiovascular disease.

This study was designed to clarify the importance of the prandial state when measuring TG levels.

Prospective study (part of the Women's Health Study) followed over 26 000 initially healthy US women over age 45 (mean age =54) enrolled between 1992 and 1995. Follow-up for 11 years. Participants were divided into those who were postprandial and those who were fasting.

Main outcome = hazard ratios for incident cardiovascular events (non-fatal MI, non-fatal ischemic stroke, coronary revascularization, or cardiovascular death).

In the fasting group, after adjusting for possible confounders, the trend of hazard ratios for cardiovascular diseases related to increasing fasting TG levels was *not* statistically significant.

In the non-fasting group, after adjusting for possible confounders, the trend of hazard ratios for cardiovascular disease was statistically significant as post-prandial TG levels rose. Event rate per 1000 person-years rose from the lowest quintile of TG to the highest (1.3 to 2.8) And hazard ratios rose from 1.0 to 2.0

“In this large-scale prospective cohort of healthy US women, we observed that higher non-fasting triglyceride levels were strongly associated with increased risk of future cardiovascular events, independent of baseline cardiac risk factors, levels of other lipids, and marker of insulin resistance.”

In contrast, fasting TG levels showed little independent association with events.

“Taken together, our results support the hypothesis that atherosclerosis is, at least in part, a ‘postprandial’ phenomenon.”

The use of non-fasting TG levels in risk assessment provides several potential advantages to clinical practice.

I believe this study is important. It clarifies the heretofore murky relation between TG and atherosclerotic disease. It may lead to another valid marker to be included in risk evaluation. Elevated TG levels are treatable.

Is TG Taking A Prominent Defined Place As A Risk Factor?

7-7 TRIGLYCERIDES AND RISK OF CORONARY HEART DISEASE

“The majority of patients with premature CHD have lipoprotein disorders that have a combination of elevated triglyceride levels, low levels of HDL-c, and atherogenic LDL-c particles—referred to as the ‘atherogenic lipoprotein phenotype’ due to a strong association with CHD risk.” This phenotype is associated with truncal obesity, and insulin resistance (ie, the metabolic syndrome). The metabolic syndrome has a prevalence of 25% in US adults, and 45% in adults older than 60.

Postprandial lipoproteins are generally triglyceride rich, and if an individual has a predisposition to producing remnant particles or small, dense LDL-c particles, or has insulin resistance, then clearance of these particles can be delayed as long as 12 hours. Prolonged exposure of the patient's endothelium to TG-rich atherogenic remnant

particles, or the associated states in which atherogenic lipoprotein particles occur (eg, obesity, the metabolic syndrome) may account for greater CHD risk.

Clinical trials testing treatment for elevated triglyceride levels may need to include the effects of both baseline and postprandial levels and to measure the effect of specific treatments on reducing postprandial lipoproteins. A simpler choice may be the use of non-HDL-cholesterol (*Non-HDL-c = Total cholesterol minus HDL-cholesterol. This measures LDL-c + TG-associated cholesterol.*) This is accurate and reliable in a non-fasting state, and would be simple to incorporate into clinical practice.

It is important to aggressively and comprehensively treat patients with dyslipidemias that include high levels of TG, low levels of HDL-c, and the presence of small LDL-c particles, using both lifestyle and medications

Does this relate to clinical benefit?

Will lowering TG levels (either fasting or non-fasting, or both) translate into reduction in risk of CHD?

I believe both are indicators of risk. Non-fasting TG should be included in the risk factor complex.

It is premature to argue which is most important. Primary care clinicians may now begin to relax their restrictions on laboratory determination of lipids and, with more convenience to the patient, draw blood in the non-fasting state. Some may wish to rely on the non-HDL-cholesterol levels.

Will lowering TG per-se (without affecting other factors) lead to benefit? Can TG be lowered without an effect on other factors? Instead of focusing on one lipid, we should focus on all facets of dyslipidemia.

Meanwhile, TG seems to be taking its rightful place as a risk factor.

A Bite A Day Keeps The Doctor Away

7-8 EFFECTS OF LOW HABITUAL COCOA INTAKE ON BLOOD PRESSURE AND BIOACTIVE NITRIC OXIDE

Cocoa is especially rich in flavanols (a subclass of polyphenols) that have been suggested to mediate the favorable effects of cocoa products on cardiovascular health and BP. The effects of cocoa flavanols may be due to enhancement of endothelial nitric oxide, thereby lowering BP.

This randomized, parallel-group trial followed 44 adults (mean age 64), for 18 weeks.. All had either pre-hypertension (BP 130/85 to 139/89), or grade 1 hypertension (BP 140/90 to 160/100). Mean BP = 147/87. None had BP more than 170/100.

Randomized to: 1) 6 grams of dark chocolate (one piece of a 16-piece bar of 100 grams commercially available chocolate) containing 30 mg of polyphenols, or 2) 6 grams of a polyphenol-free white chocolate. Both contained 30 kcal and similar macronutrients and electrolytes.

Change (mean) in BP baseline to 18 weeks:

Dark chocolate	White chocolate
- 2.9/1.9 (CI = 1.6/1.0)	No change

(BP was lowered progressively over the 18 weeks.)

Hypertension prevalence declined from 86% to 68% in the dark chocolate group. BP reductions were more pronounced in hypertensive as compared with normotensive participants.

Although the effects on BP were small, they are clinically noteworthy. On a population basis, it has been estimated that a 3-mm reduction in systolic would reduce the relative risk of stroke mortality by 8%, of coronary artery disease mortality by 5%, and of all-cause mortality by 4%.

“The most intriguing finding of this study is that small amounts of commercial cocoa confectionary convey the similar BP-lowering potential compared with conventional dietary modifications that have proven efficacy to reduce cardiovascular event rate.”

Conclusion: Intake of low habitual amounts of dark chocolate caused progressive reductions in systolic and diastolic BP in older subjects with pre-hypertension or stage 1 hypertension.”

Interest in the BP-lowering effects of cocoa has been going on for almost 2 decades. Interest is increasing. Sales of “Dark Chocolate” are growing. . This study points out that small daily doses of dark chocolate are effective in reducing BP—a possible simple, inexpensive add-on to prevention and therapy of hypertension.

Definitions according to Wikipedia:

“Cocoa” is the term used to describe a powder obtained by grinding and roasting beans of the cacao tree.

It is a combination of solids and fat (cocoa butter). It may be in the form of a liquor.

“Chocolate”: a combination of the solids and the fat. It is available in many forms and flavors.

“Dark chocolate”: chocolate without milk as an additive. The FDA requires a 15% concentration of chocolate liquor. EU regulations specify a minimum of 35% cocoa solids.

“White chocolate”: A confection based on cocoa butter (fat) without cocoa solids. Some authorities state it really should not be called “chocolate”

Thus, the beneficial contents of “dark chocolate” vary considerably. I believe chocolate or cocoa products which are somewhat dark in color contain some cacao solids and flavanols. . The amount of solids varies greatly.

Cocoa butter contains saturated fat. This raises questions about its effect on cholesterol levels. The fat is mainly comprised of stearic acid which has a neutral effect on cholesterol.

The combination of flavanols in a chocolate bar, and the lack of adverse effects of the fat content, leads me to believe that a chocolate treat is a healthy treat. According to this study, small amounts of dark chocolate (which would have no significant effect on daily caloric, fat, or glucose intake) do provide enough flavanols to lower BP.

Can Reduce Recurrence. Little Impact On Prevalence

7-9 SURGERY + COMPRESSION VS COMPRESSION-ALONE FOR VENOUS LEG ULCERS

Compression using four layer bandaging is the mainstay of treatment for leg ulcers associated with incompetent veins. It completely heals ulcers in a mean of 8 weeks when delivered by trained nurses in the community.

This long-term study compared compression alone vs compression + superficial surgery in patients with open, or recently healed leg ulcers, and superficial venous incompetence. (Most previous trials either ignored the role of compression therapy, or compared surgery with compression, which is inappropriate, as both are effective treatments that should be complementary.)

There was no significant difference between compression-alone, and surgery + compression on ulcer healing at 3 years.

Recurrence of the ulcer, which otherwise happens in a quarter of patients each year, was almost halved by surgery.

Conclusion: Surgical correction of superficial venous reflux in addition to compression bandaging did not improve ulcer healing, but reduced the recurrences of ulcers.

Impaired Ability to Read Has a Strong, Independent Association with Death.

7-10 HEALTH LITERACY AND MORTALITY AMONG ELDERLY PERSONS

This study asks: Could reading fluency have a direct effect on health?

A prospective cohort study followed over 3200 community-dwelling Medicare enrollees (mean age = 74) in 4 US centers. Interviewed subjects in 1997 to determine their demographic characteristics, chronic conditions, self-reported physical and mental health, and health behaviors.

Measured health literacy by testing reading fluency (Test of Functional Health Literacy in Adults). Scores range from 0 to 100. Scores of 0 to 55 indicate inadequate literacy. Individuals with impaired health literacy often misread the simplest materials, including prescription labels, and appointment slips. Scores of 56 to 66 indicate marginal literacy. Scores of 67 to 100 indicate adequate health literacy

A total of 815 participants died during an average follow-up of 68 months.

Crude mortality rates according to health literacy:

Adequate (n = 2094; 64%)	Marginal (n= 366; 11%)	Inadequate (n = 800; 24%)
19%	29%	39%

Hazard ratios for all-cause mortality after adjustment for several possible confounders:

1.00	1.13	1.52
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Participants with inadequate health literacy were more likely to be non-white, have less annual income and education, and to be in worse physical and mental health at baseline.

Conclusion: Inadequate health literacy, as measured by reading fluency, predicted mortality.

I abstracted this article because health literacy, although more a social problem, is partly a public health issue. Note the frequency of health illiteracy (about 25% in these community dwelling subjects). I believe many primary care clinicians do not realize the extent of this problem. Of course, it depends on the social strata of your patients.

Primary care physicians should be aware of the magnitude of the problem, and may alleviate it somewhat by attempting to ensure that their patients fully understand medical instructions. This may be accomplished by fully instructing a literate surrogate, and by asking the patient to repeat instructions after receiving them. Although time consuming we should not let patients leave the office until we are sure they understand.

Some highly literate individuals, as they age and their memories become impaired, will require as much attention to this problem as the socially disadvantaged.

From 1 in 143 To 1 in 1361

7-11 ESTIMATING RISK OF CANCER ASSOCIATED WITH RADIATION EXPOSURE FROM 64-SLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

Computed tomography coronary angiography (CTCA) has become a common diagnostic test.

It is generally perceived that a cancer risk is associated with CTCA. Few quantitative data are available. A FDA report suggested an increased risk of fatal cancer of 1 in 2000.

The recent report of the Biological Effects of Ionizing Radiation (**BIER**) provides a framework for estimating cancer risk. It incorporates data from atomic bomb survivors as well as from medical and occupational radiation studies. The data supports the so-called linear, no threshold risk model for low dose exposures to X-rays. (Ie, risk of cancer proceeds in a linear fashion with no lower threshold.)

There was a marked variation in cancer risk by age, sex, and CTCA scan protocol. Rather than a relatively constant cancer risk of 1 in 1000 or 1 in 2000, the lifetime attributable risk ranged from 1 in 5000 for an 80-year old man to nearly 1 in 100 for 20-year old women.

A long lag-time is typical from acute radiation exposure to the development of malignancy. A 12-year minimum latency from radiation exposure to excess breast cancer risk has been described in Japanese atomic bomb survivors.

“The results of this study suggest that CTCA should be used particularly cautiously in the evaluation of young individuals, especially women.” But, coronary angiography is also related to immediate and even more frequent major complications. (*Ie, clinicians and radiologists should decide the benefit / harm-cost ratio of standard angiography vs CTCA for individual patients.*)

These lifetime attributable risks are calculated on exposure to one CTCA. Risks from radiation are cumulative over a lifetime.

Conclusion: The estimated lifetime attributable risk of CTCA varies widely depending on age, sex, and protocol. Risks of cancer due to radiation are not negligible.

Note—risk applies to all radiation accumulated during a lifetime.

Primary care clinicians are involved in this dilemma, albeit indirectly. I believe it is prudent for them to consult with their referral radiologists and ask for their concerns for this problem.

Cancers resulting from radiation will not appear for years. The physician ordering the tests may not be around after this length of time, and may not have to face the accusation that they were responsible.

If a drug were found to be associated with cancer risk of this magnitude, it would be withdrawn.

FULL ABSTRACTS JULY 2007

The Recommended 'Adequate' Intakes Are Actually Inadequate

7-1 VITAMIN D DEFICIENCY

“Once foods were fortified with vitamin D and rickets appeared to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved.”

Not so. Rickets can be considered the tip of the vitamin D-deficiency iceberg. Vitamin D deficiency remains common in children and adults. In utero, deficiency can cause growth retardation and skeletal deformities. In adulthood, deficiency can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscular weakness, and increase the risk of fracture.

Most tissues and cells have vitamin D receptors. This has provided new insights into the multiple functions of the vitamin.

This long review reports progress of our understanding of the many facets of vitamin D deficiency, and suggests ways of avoiding and treating deficiency.

Sources and Metabolism of Vitamin D:

- The “D” in food labels and supplements represents D2 (ergocalciferol) or D3 (cholecalciferol). Both are used in over-the-counter supplements.
- We get most of our natural vitamin D3 from exposure to sunlight.
- Few foods naturally contain vitamin D. Few foods are fortified with vitamin D.
- Vitamin D from the skin and diet is metabolized in the liver to an inactive form, 25-hydroxyvitamin D, which in turn is metabolized by the kidneys to its active form, 1,25 di-hydroxy vitamin D. In the presence of 1,25 di-hydroxy vitamin D, absorption of calcium and phosphorus from the gut is increased.
- The metabolism of vitamin D is complex, involving the gut, liver, kidney, bone, muscle, parathyroids, as well as the skin.

Definition and Prevalence of Vitamin D Deficiency:

- Serum 25-hydroxyvitamin D is considered the assay of choice.
- “ A level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter can be considered to indicate sufficient vitamin D.”
- Vitamin D intoxication is observed when serum levels exceed 150 ng per milliliter.
- An estimated one billion people worldwide have vitamin D deficiency or insufficiency.
- According to several studies, 40% to 100% of community-dwelling elderly persons in the USA are deficient. More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels (< 30 ng per milliliter of 25-hydroxyvitamin D).
- Fifty % of children have been reported to have levels under 20 ng per milliliter.

- One third of healthy students, physicians, and residents at a Boston hospital were found to be deficient, despite drinking a glass of milk and taking a multivitamin daily, and eating salmon at least once a week.
- Pregnant and lactating women are often deficient despite taking a multivitamin containing 400 IU.
- Even in the sunniest areas, deficiency is common when most of the skin is shielded.

Calcium, Phosphorus, and Bone Metabolism:

- Without vitamin D, only 10-15% of dietary calcium is absorbed from the gut.
- The interaction of 1,25 di-hydroxyvitamin D with the receptor in the intestine increases calcium absorption to 30-40%.
- When the serum level of 25-hydroxyvitamin D falls below 30 ng/mL, there is a significant decrease in intestinal calcium absorption. As vitamin D deficiency progresses, the parathyroid glands are stimulated, causing secondary hyperparathyroidism. The hormone activates osteoclasts which dissolve the mineralized collagen matrix in bone, causing osteopenia and osteoporosis. The hormone also causes phosphaturia, and a low serum phosphorous. The calcium-phosphorous product becomes inadequate; mineralization of the collagen matrix of bone is diminished, leading to the classical signs of rickets in children and osteomalacia in adults.
- One study showed that 93% of persons age 10 to 65 admitted to a hospital emergency department with muscle aches and bone pain with a wide variety of diagnoses (including fibromyalgia, chronic fatigue syndrome, and depression) were deficient in vitamin D.

Osteoporosis and fractures:

- About 1/3 of women age 60 to 70, and 2/3 of women over age 80 have osteoporosis.
- An estimated 47% of women, and 22% of men over age 50 will sustain an osteoporotic fracture in their remaining lifetime.
- Among 3200 women in France who received 1200 mg calcium and 800 IU of vitamin D3 daily over 3 years, risk of hip fracture was reduced by 43%.
- A meta-analysis evaluating the risk of fracture in older persons given 400 IU of vitamin D3 daily revealed little benefit in risk of fracture. In studies using 700 to 800 IU vitamin D3, hip fracture was reduced by 26% as compared with calcium supplements or placebo.
- Optimal prevention of fracture occurred only in trials providing 700 to 800 IU of vitamin D3 daily in patients whose baseline serum 25-hydroxyvitamin D level was low (< 17 ng/mL), and whose mean concentrations rose to 40 ng/mL.

Muscle Strength and Falls:

- Vitamin D deficiency causes muscle weakness.
- Skeletal muscles have vitamin D receptors and may require vitamin D for maximum function.
- Performance speed and proximal muscle strength markedly improved when serum levels of

25-hydroxyvitamin D increased from low levels to over 40 ng/mL.

- A meta-analysis reported that increased serum levels reduced the risk of falls by 22% compared with calcium or placebo.
- 400 IU of D3 was not effective in preventing falls; 800 IU D3 plus calcium reduced the risk of falls.

Non-skeletal Actions of Vitamin D

- Brain, prostate, breast, colon, and immune cells have vitamin D receptors.
- Directly or indirectly, 1,25 di-hydroxyvitamin D controls more than 200 genes.
- Lower serum levels are related to increased incidence of colon cancer and breast cancer, multiple sclerosis, rheumatoid arthritis, and osteoarthritis as well as hypertension and cardiovascular disease.

Vitamin D Requirements and Treatment Strategies:

- The Institute of Medicine recommends 400 IU for adults age 61-70 and 600 IU for over 70. Most experts agree that without adequate sun exposure, the requirements are 800 to 1000 IU daily. (*D2 or D3 not specified. I presume D3 RTJ*)
- Vitamin D2 is about 30% as effective as vitamin D3 in maintaining 25-hydroxyvitamin D levels; up to 3 times as much may be required to maintain sufficient serum levels.
- A cost effective method for correcting deficiency and maintaining adequate levels is to give 50 000 IU of D2 once a week for 8 weeks followed by 5000 IU (available by prescription) every 2 to 4 weeks thereafter, or 1000 IU of D3 daily (available in most pharmacies) or 3000 IU of D2 daily.
- 100 000 IU of D3 once every 3 months is effective in maintaining 25-hydroxyvitamin D levels at 20 ng/mL or higher.
- Lactating women given 4000 IU of D3 daily had an increase in the level of 25-hydroxyvitamin D to more than 30 ng/mL and were able to transfer enough to satisfy their infant's requirement.
- Patients with malabsorption of fat require higher doses.
- Depending on time of day, season, latitude, and skin pigmentation, 5 to 30 minutes of sun exposure between 10 AM and 3 PM twice a week is sufficient. The skin has a great capacity to make vitamin D3 even in the elderly, and will reduce risk of fracture.
- Tanning beds are an excellent means of treating and preventing deficiency.

Vitamin D intoxication:

- Is extremely rare. Doses of more than 50 000 IU daily raise 25-hydroxyvitamin D levels to more than 150 ng/mL, causing hypercalcemia and hyperphosphatemia.
- Doses of 10 000 IU of D3 daily up to 5 months do not cause toxicity.

Conclusions:

- Undiagnosed vitamin D deficiency is common.
- Serum level of 25-hydroxyvitamin D is the barometer for vitamin D status.
- Serum 25-hydroxyvitamin D not only predicts bone health, it also is an independent predictor of

risk of cancer and other chronic diseases. “The report that postmenopausal women who increase their vitamin D intake by 1100 IU of vitamin D3 reduce their relative risk of cancer by 60 to 77% is a compelling reason to be vitamin D-sufficient.”

- Most commercial assays for 25-hydroxyvitamin D are good for detecting deficiency. Radio-immunoassays measure total 25-hydroxyvitamin D which includes 25-hydroxyvitamin D2, and 25-hydroxyvitamin D3. As long as the combined total is 30 ng/mL or more, the patient has sufficient vitamin D.
- Because serum assay is costly, and may not always be available, providing children and adults with at least 800 IU of D3 per day, or its equivalent, should guarantee sufficiency.
- “Much evidence suggests that the recommended ‘adequate’ intakes are actually inadequate, and need to be increased to at least 800 IU of D3 daily. It is very difficult to obtain that much D3 on a daily basis from dietary sources.”

NEJM July 19, 2007; 357: 26-81 “Medical Progress”, review article by Michael F Holick, Boston University Medical Center, Boston, Mass.

Recap: To clarify::

1. “Vitamin D” can mean either D2 or D3:

D2 (ergocalciferol) is manufactured through ultraviolet irradiation of ergosterol from yeast.

D3 (cholecalciferol) is manufactured by ultraviolet irradiation of 7-dehydrocholesterol from lanolin. It is the form made naturally in the body by action of sunlight. (Ultraviolet B radiation ~ 300 nm) converts 7-dehydrocholesterol into D3.)

2. Few foods naturally contain vitamin D. Fortified foods almost always contain D3.
3. Both D2 and D3 are used in over-the-counter tablets. An over-the-counter multivitamin tablet contains 400 IU (25 ng) vitamin D (either D2 or D3). Over-the-counter vitamin D3 contains varying amounts up to 2000 IU. The form available in the US by prescription is D2.
4. The distinction between D2 and D3 is important. D3 is about 3 times as powerful in production of 25-hydroxyvitamin D. I would make sure the form in the tablet or in fortified foods is D3
5. Both D2 and D3 are readily converted by the liver to 25-hydroxyvitamin D. This circulating form is used to determine patients’ vitamin D status. 25-hydroxyvitamin D is inactive.
6. Reference range for 25-hydroxyvitamin D:

Deficiency	Preferred	Intoxication
< 20 ng/mL	30-60 ng/mL	>150 ng/mL

(The threshold for effective fracture prevention is thought to be 30 ng/mL.)

7. The kidney converts inactive 25-hydroxyvitamin D to the active form of the vitamin--1,25 di-hydroxyvitamin D.

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A Vitally Important Public Health Issue

7-2 REDUCING THE POPULATION BURDEN OF CARDIOVASCULAR DISEASE BY REDUCING SODIUM INTAKE A Report of the Council on Science and Public Health of the AMA

Nearly 30% of US adults have hypertension (defined as 140/90 and above), and/or use of antihypertension drugs. Another 1/3 have pre-hypertension (120-139/80-89). The risks of developing cardiovascular disease (CVD) rise progressively as BP rises above 115/75.

The risk of developing hypertension derives from the effects of many factors in heredity and environment. Salt intake is an important component.

This review evaluates the scientific underpinning for reducing salt intake¹ to decrease the public health burden of hypertension.

With few exceptions, observational studies examining various non-industrialized societies have correlated salt intake with the increased incidence of hypertension, or showed that, when salt was introduced into the diet, the prevalence of hypertension increased. Primitive societies with habitually low salt intake are normotensive and do not exhibit increases in BP with age. When they migrate, and adopt more modern lifestyles and increase salt intake, BP levels increase.

The Intersalt study (10 000 subjects age 20-59; 52 centers) assessed the relationship between 24-hour urinary sodium excretion and BP. Populations with a salt intake of less than 3 grams daily had low BP, and little or no increase in BP with age. There was a linear relation between systolic BP and 24-h sodium excretion.

The International Study on Macronutrients and Blood Pressure found a lower salt intake, and a reduction in the ratio of sodium / potassium translated into a lower average population BP.

About 100 randomized controlled trials examining the effect of reducing salt intake on BP in normotensive and hypertensive individuals found that reducing salt intake lowered BP. Meta-analysis of 11 RCTs of patients at over age 60 concluded that a long-term high salt diet increased mean BP by 6/4 mm Hg.

The DASH-sodium trial of diets (fruits, vegetables, low fat, more potassium, fiber, and protein) combined with varying degrees of salt intake reported that the degree of salt restriction was related to greater BP reductions:

	BP reduction
DASH + 8 grams salt	- 6/3
DASH + 6 grams salt	- 7/4
DASH + 3 grams salt	-10/5

Salt intake is an independent predictor of left ventricular mass. With high dietary salt, platelet activity increases. A low salt diet reduces aortic stiffness and increases compliance.

In the US, the average daily intake of salt in adults is now estimated to be about 10 grams per 2000 kcal. Between 1970 and today, salt intake has increased by 55%. (As the obesity epidemic flourished in America, the increased caloric intake was associated with increased salt intake.)

About 80% of daily intake of salt comes from processed foods. Some canned and processed foods contain

one gram of salt per 8 ounce serving. Restaurant meals can contain as much as 6 to 12 grams of salt (See table 3 page 1464 for a detailed list of sodium content of various foods.)

Fostering behavioral changes in natural settings is difficult. Maintaining salt restriction, even in supervised RCTs, wanes over time in the absence of readily available foods with lower salt content. The long-term effect of physician-advice to reduce salt intake in a natural setting is severely constrained.

Global efforts are being made to address the problem of excess salt intake:

WHO: Recommends an average daily salt intake in adults of less than 5 grams, and urges government efforts to reduce the amount of salt added to processed foods.

England: Began a major campaign in 2003 to encourage the food industry to reduce added salt with a recommendation that individuals consume less than 6 grams of salt daily.

Ireland: Has developed a national program to reduce mean salt consumption in adults to 6 grams daily, and is seeking cooperation from the food industry.

New Zealand/Australia: Created a labeling program which identifies foods that meet standards for salt content.

France: Has a goal of reducing BP by 10 mm Hg in part by reducing salt intake by 20%.

Finland: Since the 1970s, Finland's focus on reducing salt intake has been associated with a 30% decline in average daily intake from 12 grams to 8 grams. Labeling is required as "high salt" if a food exceeds specific limits. Population-wide decrease in the ratio of dietary sodium to potassium has been associated with an average population decrease in diastolic BP of about 10 mm Hg. Deaths from stroke and ischemic heart disease among 30 to 59-year olds has decreased 60%.

USA: Salt reduction is a cornerstone of the National High BP Education Program which recommends limiting salt intake to 6 grams daily. The National Academy of Sciences recently established a tolerable upper intake of less than 6 grams. It concluded that a daily intake of salt of 4 grams is adequate in healthy 19 to 50 year-olds, and even lower levels are adequate for older populations. The FDA "Nutrition Facts" food labels set a daily intake of salt of 6 grams regardless of caloric intake.

Salt levels often vary widely among different brands of the same foods, indicating that manufacturers could lower levels without jeopardizing marketability. Huge variations in salt content in food products made by the same manufacturer occur with no obvious rationale.

Food manufacturers can add substantial amounts of salt to processed foods on the basis of the FDA designation of salt as an ingredient that is "generally regarded as safe". (GRAS) A suit has been filed to force the FDA either to affirm sodium's current GRAS status, or to approve salt as a food additive at specified levels in various types of food.

Substantial public health benefits accrue from small reductions in the population-BP. Reductions are achievable by lowering salt intake. Any meaningful strategy to lower salt intake must rely on food manufacturers and preparers. This can be accomplished without inconvenience or loss of food enjoyment.

Archives Int Med July 23, 2007; 167: 1460-68 “Special article” a report from the AMA Council on Science and Public Health. first author Barry D Dickinson, Secretary to the Council on Scientific Affairs, AMA. .

1 The article often refers to sodium content rather than salt (NaCl). I have converted sodium to salt for simplicity and clarity. Most of the dietary sodium intake is in the form of salt. Restriction of salt intake is the only means of reducing the burden of sodium.

To calculate conversion of sodium into salt (NaCl);

Mol weight Na = 23; of Cl = 35; NaCl = 58

Multiply Na in grams by 2.5 to obtain NaCl in grams.

One teaspoon of salt weight about 6 grams.

Continued Evaluation In Clinical Practice Is Required To Determine The Role Of This New Class Of Drugs

7-3 EFFICACY AND SAFETY OF INCRETIN THERAPY IN TYPE 2 DIABETES: A Systematic Review and Meta-analysis

“Incretin” is the generic name of all insulinotropic substances originating in the g.i. tract in response to ingestion of glucose.

Efficacy of available therapies for type 2 diabetes mellitus (DM-2), even when used appropriately, diminishes as the disease progresses because of a steady, relentless decline in pancreatic beta-cell function. Current therapies are often limited by adverse effects such as weight gain and hypoglycemia. Most do not target postprandial hyperglycemia effectively. “Therapies targeting the decline in beta-cell function without causing weight gain and with minimal adverse effects are desirable.”

The improved understanding of the incretin effect on the pathophysiology of DM-2 has led to development of new hypoglycemic agents.

Incretins:

- 1) An oral glucose load is more effective at releasing insulin than the same amount of glucose given intravenously. This observation led to the evolution of understanding the incretin effect.
- 2) Incretins are peptides normally secreted by the intestine, released in response to glucose nutrients in the gut.
- 3) Incretins depend on glucose concentrations. Secretion ceases when serum glucose level is less than 55 mg/dL.
- 4) Incretins are composed primarily of 2 peptides which lower blood glucose levels:
 - A. An insulinotropic peptide increases insulin production and release from the pancreas.
 - B. A glucagon-like peptide impairs the normal action of glucagon and inhibits release of glucose from the liver.

5) Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase. The half life of incretins is normally very short.

The incretin pathway appears to be attenuated in DM-2. This makes the pathway an attractive target for development of new drugs:

- 1) Incretin mimetics: The first incretin mimetic, exenatide (Byetta; Amylin), was approved in 2005. This is a chemical analogue of incretin which is resistant to degradation by the peptidase. Its action is prolonged. It requires injection. It is used as “add on” therapy.
- 2) Incretin enhancers: Inhibit the peptidase which degrades incretin, thus extending the half-life of native incretins, and prolonging their effects. In October 2006, the FDA approved the first oral incretin enhancer, sitagliptin (Januvia; Merck). It is used as monotherapy, or with metformin or a thiazolidinedione.

This meta-analysis assessed the efficacy and safety of an incretin mimetic and an incretin enhancer in non-pregnant adult patients with DM-2. The analysis was based on randomized trials.

Conclusion: Incretin therapy offers an alternative to currently available hypoglycemic agents for non-pregnant patients with DM-2.

STUDY

1. Twenty nine randomized, controlled trials met inclusion criteria. All reported original data from controlled trials in patients with DM-2. Diabetes control at baseline was considered poor (HbA1c ~ 8%).
2. Duration of all studies was 12 weeks or more. (A shorter duration would inadequately assess glycemic efficacy, as HbA1c reflects glycemia during the previous 12 weeks.)
3. Two different drugs having incretin-like properties were included: 1) exenatide (Byetta; Amylin), and 2) sitagliptin (Januvia; Merck).

RESULTS

1. Byetta is an incretin mimetic (a chemical analogue of incretin):
 - 1) Patients with DM2 were divided into 2 groups:
 - A. Various combinations of sulfonylurea, metformin, and/or a thiazolidinedione + placebo injections
 - B. Various combinations of sulfonylurea, metformin, and/or a thiazolidinedione + Byetta injections.
 - (Note: Byetta is not given as monotherapy.)
- 2) Compared with placebo, mean decline in HbA1c = -1.0% favoring Byetta. Patients receiving Byetta were more likely to achieve a HbA1c < 7% than those receiving placebo (45% vs 10%).
- 3) Fasting glucose and postprandial glucose also were reduced. .
- 4) Compared with insulin glargine or aspart there was no difference in reduction of HbA1c.

- 5) Subjects in the Byetta groups lost weight. Weight change Byetta vs placebo = - 1.4 kg;
vs insulin = - 4.8 kg
 - 6) Adverse effects: hypoglycemia requiring assistance occurred in only 5 out of 2781 patients, and only in those also receiving a sulfonylurea. Nausea, vomiting, and diarrhea were common, leading to withdrawal of 4% of participants.
2. Januvia an incretin enhancer—enhances the duration and activity of natural incretins by blocking the enzyme (a peptidase) which normally degrades incretins.
- 1) Patients with DM2 received::
 - A. Januvia alone vs placebo (5 trials), or
 - B. Januvia + metformin vs metformin + placebo, or
Januvia + thiazolidinedione vs thiazolidinedione + placebo, or
Januvia + placebo vs metformin + glipizide + placebo
 - 2) Januvia was associated with a lowering of HbA1c by a mean of -0.74%. Efficacy was similar when Januvia was used as mono-therapy as with add-on therapy.
 - 3) Januvia patients were more likely to achieve a HbA1c of less than 7% (43% vs 17% for placebo).
 - 4) Fasting glucose and postprandial glucose also were reduced.
 - 5) Weight: Slight increase with Januvia (+0.5 kg) compared with placebo. Less weight gain compared with glipizide. Metformin was associated with weight loss. (- 2.2 kg)
 - 6) Adverse effects: Severe hypoglycemia occurred in 2 patients receiving Januvia alone. No increase in g.i. adverse effects compared with placebo. Januvia was “very well tolerated”.

DISCUSSION

1. “The introduction of a new class of medications is generally a welcome addition to the existing armamentarium against type 2 diabetes.” “However, new medications are prized and are often quickly embraced over older, well-established, and effective medications despite limited ability to judge the merits of new medications in relation to long-term effectiveness and safety soon after approval for clinical use.”
2. Aggressive marketing campaigns and direct-to-consumer advertisements contribute to use of new medications.
3. These new drugs are moderately effective in improving glycemia. (HbA1c levels are lowered by ~ 1%) They have neutral or favorable effects on weight. Nearly all other available hypoglycemic agents (except metformin) cause weight gain.
4. Byetta is associated with g.i. adverse effects. Nausea was possibly related to delay in gastric emptying. Januvia has a slightly increased risk of nasopharyngitis and urinary tract infections and headache. About 20% of participants withdrew during the trials.
5. “The preferential improvement in postprandial glycemia with incretin therapy addresses an important

limitation of currently available pharmacological therapies, and provides an alternative to our limited options.”

6. The low hypoglycemic event rate offers an advantage, and confirms the glucose-dependent action of incretins.
7. Long-term efficacy and safety are not known.

CONCLUSION

Incretin therapy offers an alternative to currently available hypoglycemic agents in non-pregnant adults with type 2 diabetes. Efficacy is modest. Effects of weight are favorable.

Careful postmarketing surveillance for adverse effects and continued evaluation in clinical practice are required to determine the role of this new class of drugs for treatment of DM-2.

JAMA July 11, 2007; 298: 194-206 Systematic review, first author Renee E Amori, Tufts-New England Medical Center, Boston, Mass.

The article considered several other incretin mimetics and enhancers. I limited this abstract to two available drugs.

These drugs are not to be used in children or during pregnancy.

Completely New; Few Adverse Effects

7-4 PHARMACOLOGY OF BYETTA AND JANUVIA Incretin Mimetic And Incretin Enhancer: A Review

These drugs for the treatment of DM-2 are completely new. Their action is unique. They have modest HbA1c-lowering ability. They will likely be “add on” drugs rather than used alone. They have major advantages: 1) less risk of hypoglycemia, and 2) less weight gain. Thus far, no serious adverse effects have been reported.

Primary care clinicians should be familiar with their action and use, and their benefit / harm–cost ratio. Patients will be asking about them and may be requesting their prescription. Similar drugs from different drug companies will be forthcoming.

This article reviews some of their pharmacological properties in more detail.

1 Byetta (exenatide; Amylin)

An incretin mimetic. It contains 39 amino acids, the sequence of which partially overlaps that of natural incretin. It binds to, and activates, incretin receptors. Normal incretins act transiently (only minutes) after a rise in blood glucose. Byetta is resistant to degradation by the enzyme (a peptidase) which rapidly degrades naturally produced incretins. Plasma concentrations of Byetta, after subcutaneous injection, peak at 2 hours and are still detectable at 10 hours. Elimination is by the kidney. It should not be used in patients with substantially decreased creatinine clearance.

It mimics the action of incretin:

- 1) Increases glucose-dependent insulin synthesis and secretion by the pancreatic beta-cells, but only in the presence of increased blood glucose. It restores the normal first phase insulin release (immediate—within minutes) which is lost in DM2. And it increases the 2nd phase (longer lasting) secretion of insulin, decreasing the fasting and postprandial blood glucose.
- 2) Decreases secretion of glucagon, resulting in decreased glucose production by the liver. It does not impair the normal glucagon response to hypoglycemia.
- 3) Slows gastric emptying and decreases appetite and food intake. Weight loss may occur.

In patients with DM2 who have not achieved good glucose control, it is indicated as adjunctive therapy (in addition to metformin, a sulfonylurea, or both). It is not used alone. Concurrent use with a thiazolidinedione and insulin not yet indicated.

Administered by subcutaneous injection twice daily (in microgram amounts) before morning and evening meals. Do not give after meals. Available in a prefilled pen, which supplies 60 injections. A month's supply cost over \$200.

Adverse effects:

Nausea and vomiting, diarrhea, dizziness. (Rarely severe enough to cause withdrawal.)

It is “generally well tolerated”

Hypoglycemia may occur when used in addition to a sulfonylurea, but not with metformin.

It does not alter the counter-regulatory hormone response to hypoglycemia.

No additional adverse effects in the elderly

Not indicated in pregnancy.

2. Januvia (sitagliptin; Merck)

An incretin enhancer. It is a potent and highly selective inhibitor of the peptidase which degrades natural incretins. The physiological action of the natural incretins is boosted, and their half-life prolonged. The resultant enhanced beta-cell secretion of insulin, and the decreased glucagon production, act in concert to lower glucose levels. The effect in lowering HbA1c levels is greater in patients with higher baseline levels.

It has little action when blood glucose levels are normal. It is active only when blood glucose levels are higher than normal.

Can be used as monotherapy, or with metformin or a thiazolidinedione. Not to be used with sulfonylureas (more hypoglycemia)

Given by mouth once daily. Lowers HbA1c modestly. Also lowers fasting plasma glucose, and 2-hour pc glucose.

Adverse effects: “Generally well tolerated”. No increase in incidence of gastrointestinal adverse events.

Runny nose, sore throat, headache, g.i. upset, and increased incidence of urinary tract infections.

Hypoglycemia reported rarely. No weight gain. Dose must be adjusted in patients with renal impairment.

Not to be used in pregnancy.

It is expensive. Over \$4 for a 100 mg pill

Practical Pointers July 2007, [7-2] Review article by the editor of Practical Pointers, based on data gathered from the PDR, and information on a Merck website.

Tricyclic Antidepressants Still First Choice

7-5 EFFECTS OF TREATMENTS FOR SYMPTOMS OF PAINFUL DIABETIC NEUROPATHY:

A Systematic Review

Diabetic neuropathy (DN) is common, frequently accompanied by pain. Tight glycemic control has been shown to be effective in slowing progression of DN. Antidepressants and anticonvulsants are commonly used to reduce the intensity of pain.

This systematic review explored the effectiveness of various treatments in managing painful DN.

Conclusion: The authors developed an algorithm for treatment.

STUDY

1. This systematic review included 25 randomized controlled trials comparing various drugs with a placebo.
2. Trials included antidepressants (n = 94), anticonvulsants (n = 1270), opioids (n = 329), duloxetine (*Cymbalta*; a new antidepressant; n = 805), capsaicin (n = 277).
3. Defined clinical success as a 50% reduction in pain. This was the number of patients with “moderate”, “good”, or “notable” improvement in global assessment of treatment, or at least moderate pain relief.
4. Calculated odds ratios for achievement of 30% and 50% reduction in pain. And for withdrawal due to adverse events.

RESULTS

1. Antidepressants: Four trials (n =94). Treatment period = 3 to 6 weeks.

A. Tricyclic antidepressants: desipramine (*Norpramin*) , imipramine (*Tofrani*), and amitriptyline. (*Generic*)

	Tricyclic antidepressants
Pooled odds ratio of treatment efficacy	22.0
Pooled odds ratio for withdrawal	2.3

(Odds ratios were drug vs placebo.)

The most common adverse effects were dry mouth and sedation.

B. Selective serotonin, norepinephrine reuptake inhibitor: duloxetine (*Cymbalata*)

Odds ratio of treatment efficacy	3.5
Odds ratio for withdrawal	5.6

2. Anticonvulsants: Ten trials (N = 1576). Treatment period = 2 weeks to two months.

Traditional anticonvulsants included sodium valproate (*Depacon*) , gabapentin (*Neurontin*), carbamazepine

(*Tegretol*).

Newer anticonvulsants included pregabalin (*Lyrica*) and oxcarbazepine (*Trilepta*).

	Traditional	Newer
Pooled odds ratio of treatment efficacy	5.3	3.3
Pooled odds ratio for withdrawal	1.5	3.0

Common adverse effects were somnolence and dizziness. Major adverse reaction was liver dysfunction (two patients).

3. Opioids: Three trials (n= 329). Included oxycodone and tramadol.

	Oxycodone	Tramadol
Pooled odds ratio of treatment efficacy	4.2	3.8
Pooled odds ratio for withdrawal from both	4.0	

The most common adverse effects were constipation, nausea, dyspepsia, and headache. Although tramadol was associated with improvement, the withdrawal rate was comparatively high.

4. Capsaicin topical cream: One trial (n = 277)

Odds ratio of treatment efficacy	2.4
Odds ratio for withdrawal	4.0

The most common adverse effects were burning at the site of application, cough, accidental irritation to other parts of the body, and rash.

5. Several other drugs were included in small trials, or were ineffective. (*I omitted this information. RTJ*)

DISCUSSION

1. Tricyclic antidepressants, traditional anticonvulsants, and opioids have better efficacy than newer generation anticonvulsants for relieving pain.
2. The withdrawal rate for newer generation anticonvulsants was higher than for traditional anticonvulsants.
The odds ratio for 50% relief of pain favored the traditional drugs.
3. Treatment periods were less than 6 months. Long-term effects cannot be judged.
4. In the clinical setting, management of neuropathic pain focuses on two aspects: glycemic control, and reduction in pain.
5. The authors offer a treatment algorithm based on effectiveness and adverse effects. In order:
 - A. Tricyclic antidepressants (Some patients may wish to try capsaicin first)
 - B. Traditional anticonvulsants (sodium valproate; carbamazepine)
 - C. Newer anticonvulsants (pregabalin; gabapentin)
 - D. Duloxetine
 - E. Opioid

CONCLUSION

Antidepressants and anticonvulsants are still the options most commonly used for treatment of painful diabetic neuropathy.

Long-term efficacy is not known.

BMJ July 14, 2007; 335: 87-90 Original investigation, systematic review, first author Man-chun Wong, United Christian Hospital, Hong Kong.

Is Atherosclerosis, At Least In Part, A “Postprandial Phenomenon”?

7-6 FASTING COMPARED WITH NON-FASTING TRIGLYCERIDES AND RISK OF CARDIOVASCULAR EVENTS IN WOMEN

The importance to triglycerides (TG) as a risk factor for atherosclerotic disease remains controversial. This reflects the fact that, due to the inverse correlation of TG levels with those of HDL-C, adjustment for HDL-C attenuates the relationship between TG and cardiovascular disease.

A second aspect of the controversy stems from the manner in which TG levels are typically measured. Current guidelines recommend that blood for lipid profiles be drawn after an 8 to 12 hour fast. Because TG levels can increase substantially postprandially, fasting levels ostensibly avoid the variability associated with meals and provide a more stable estimate for risk assessment.

However, postprandial lipids may play an important role in the pathogenesis of cardiovascular disease because postprandial TG-rich remnant lipoproteins [TG-associated-C = Total-C – (LDL-c + HDL-c)] can penetrate the endothelial cell layer, and reside in the subendothelial space, where they can contribute to the formation of foam cells, a hallmark of early atherosclerosis.

Elevated postprandial levels of TG also might represent an abnormal response to an oral fat load that reflects insulin resistance, a condition associated with a host of metabolic abnormalities that predispose an individual to cardiovascular disease.

This study was designed to clarify the importance of the prandial state when measuring TG levels.

Conclusion: Non-fasting TG levels were independently associated with incident cardiovascular events. Fasting levels were not.

STUDY

1. Prospective study (part of the Women’s Health Study) followed over 26 000 initially healthy US women over age 45 (mean age =54) enrolled between 1992 and 1995. Follow-up for 11 years.
2. Participants whose last meal was 8 or more hours prior to the blood draw comprised the fasting cohort (n = 20 000), and those who had eaten within 8 hours comprised the non-fasting cohort (n = 6000).
3. Measured TG levels at the time of enrollment.
4. All participants provided baseline demographic data and health history, and a blood sample

at enrollment.

5. Main outcome = hazard ratios for incident cardiovascular events (non-fatal MI, non-fatal ischemic stroke, coronary revascularization, or cardiovascular death).

RESULTS

1. The median baseline (interquartile range) of TG:

Fasting = 115 mg/dL (81-169)

Non-fasting = 133 (93-196)

2. Among both fasting and non-fasting participants, women with higher TG levels were likely to have other cardiac risk factors and markers of the metabolic syndrome. No difference between groups in alcohol use, exercise frequency, total cholesterol, HDL-C, body mass index, or glycated hemoglobin.
3. During 11 years of follow-up, 1000 participants (4%) experienced a first cardiovascular disease (CVD) event (overall event rate = 3.5 per 1000 person-years).
4. Association of TG with incident CVD (participants divided into quintiles):

- A. Fasting participants ~ 4000 per quintile:

	1	2	3	4	5
TG (mg/dL)	<74	74-98	99-132	133-184	>184
No. of events	61	87	115	155	241
Event rate per 1000 person-years	1.4	2.0	2.6	3.5	5.5
Hazard ratio (adjusted)	1.0	1.9	1.4	1.1	1.3

In the fasting group, after adjusting fully for possible confounders (total and HDL cholesterol, and measures of insulin sensitivity), the trend of hazard ratios was not statistically significant.

- B. Non-fasting participants (~ 1200 per quintile):

	1	2	3	4	5
TG (mg/dL)	<86	86-113	114-154	155-214	>214
No. of events	18	20	43	47	87
Event rate per 1000 person-years	1.3	1.5	1.8	1.7	2.8
Hazard ratio (adjusted)	1.0	0.9	1.6	1.6	2.0

In the non-fasting group, after adjusting fully for possible confounders, the trend of hazard ratios was statistically significant.

5. In analyses stratified by postprandial time, women who had eaten 2 to 4 hours prior to phlebotomy had the strongest association between TG levels and cardiovascular events.

DISCUSSION

1. "In the large-scale prospective cohort of healthy US women, we observed that higher non-fasting

triglyceride levels were strongly associated with increased risk of future cardiovascular events, independent of baseline cardiac risk factors, levels of other lipids, and marker of insulin resistance.” In contrast, fasting TG levels showed little independent association with events.

2. The association was particularly strong among individuals who had their blood drawn 2 to 4 hours after a meal. (Levels of TG and remnant lipoprotein concentrations typically peak at 4 hours.)
3. The investigators suggest several biological mechanisms for the association between postprandial TG levels and CVD:

Following food consumption, TGs are transported from the small intestine via chylomicrons through the bloodstream. Lipolysis of the TG within the chylomicrons, catalyzed by lipoprotein lipase in tissues, transforms these particles into atherogenic, triglyceride-rich remnant lipoproteins.

An elevated postprandial TG level, reflecting either a higher peak level, or a delay in clearance, can lead to an accumulation of these atherogenic particles.

4. “Taken together, our results support the hypothesis that atherosclerosis is, at least in part, a ‘postprandial’ phenomenon.”
5. High TG levels are one manifestation of the constellation of metabolic disturbances associated with insulin resistance and the metabolic syndrome. Elevated postprandial TG levels may represent an abnormal response to an oral fat load due to insulin resistance.
6. “We believe that the current data demonstrating strong differences between non-fasting triglycerides levels in terms of vascular risk-prediction may help to explain inconsistencies in previous triglyceride studies.” By emphasizing fasting TG measures, the overall association between plasma TG and vascular risk may be systematically underestimated.
7. The use of non-fasting TG levels in risk assessment provides several potential advantages to clinical practice:

Much of the 24-h day is spent in the non-fasting state. If post prandial TGs are biologically active in atherogenesis, measurement of fasting levels may provide an inadequate representation of vascular risk.

Postprandial levels are a more robust indicator of cardiovascular risk, perhaps because the greater variability of postprandial levels captures important information about an individual’s metabolism.

At a practical level, the use of non-fasting TG and the availability of assays to directly measure LDL-C levels could allow patients to have blood for a lipid profile drawn without the need to return to the laboratory after a fast.

Measuring TG levels 2 to 4 hours postprandial suggests that a “triglyceride tolerance test”, using a standardized meal warrants further evaluation as a potential indicator of a metabolic state predisposing to higher risk.

To date, almost all clinical trials of pharmaceutical agents targeting TG levels have

relied on fasting levels. These trials might have targeted the wrong patient population. Several drugs lower postprandial TG levels (eg, statins, fibrates, niacin). Future endpoint reduction trials of TG lowering agents might consider participant-inclusion based on non-fasting levels.

CONCLUSION

In this cohort of initially healthy women, non-fasting TG levels were associated with incident cardiovascular events, independent of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance. By contrast, fasting TG levels showed little independent relationship.

JAMA July 18, 2007; 298: 309-316 Original investigation, first author Sandeep Bansal, Brigham and Women's Hospital, Boston Mass.

See also "Non-fasting Triglycerides and Risk of Myocardial Infarction, Ischemic Heart Disease, and Death in Men and Women" JAMA July 18, 2007; 299-308 Original investigation, first author Borge G Nordestgaard, Herlev University Hospital, Herlev, Denmark

This study is similar. Over 7500 women and over 6000 men were followed for 26 years. With increasing levels of non-fasting TG, levels of remnant lipoproteins increased.

Adjusted hazard ratios for CHD rose as non-fasting TG rose--similar to the above study.

Is TG Taking A Prominent Defined Place As A Risk Factor?

7-7 TRIGLYCERIDES AND RISK OF CORONARY HEART DISEASE

(This editorial comments and expands on the preceding study.)

A high TG levels is associated with abnormal lipid metabolism, as well as with other CHD risk factors (obesity, insulin resistance, diabetes, and low HDL-c). How important is it to know which comes first—high TG levels, or the risk factors that cause high levels? The question remains—are high TGs or the risk factors associated with high levels of TG the most important? The risk associated with elevated TG levels may be more a function of the associated lipoprotein disorders than a direct correlation with TG levels..

Not all TG-rich lipoproteins are associated with atherosclerosis. Minimal atherosclerotic risk is reported for patients with hyper-chylomicronemia (type V), even though TG levels may exceed 1000 mg/dL. This is likely due to the presence of large lipoprotein particles associated with these disorders. (The primary risk is pancreatitis, due to high serum viscosity.)

The metabolic abnormalities associated with moderate hyper-triglyceridemia (150 to 800 mg/dL) are likely related to the types of TG-rich lipoproteins and the presence of small dense LDL-c particles. TG-rich remnant particles and small dense LDL-c particles are highly atherogenic. Small dense LDL-c particles are more likely to penetrate the arterial endothelium, and to be taken up by macrophages, than are large LDL-c particles.

Risk reduction achieved by statins have been correlated with moderate changes in TG levels and modest effects on HDL-c. “The majority of patients with premature CHD have lipoprotein disorders that have a combination of elevated triglyceride levels, low levels of HDL-c, and atherogenic LDL-c particles—referred to as the ‘atherogenic lipoprotein phenotype’ due to a strong association with CHD risk.” This phenotype is associated with truncal obesity, and insulin resistance (ie, the metabolic syndrome). The metabolic syndrome has a prevalence of 25% in US adults, and 45% in adults older than 60.

Postprandial lipoproteins are generally triglyceride rich, and if an individual has a predisposition to producing remnant particles, or small, dense LDL-c particles, or has insulin resistance, then clearance of these particles can be delayed as long as 12 hours. Prolonged exposure of the patient’s endothelium to TG-rich atherogenic remnant particles, or the associated states in which atherogenic lipoprotein particles occur (eg, obesity, the metabolic syndrome) may account for why postprandial increases in TG levels account for greater CHD risk.

Clinical trials testing treatment for elevated triglyceride levels may need to include the effects of both baseline and postprandial levels, and to measure the effect of specific treatments on reducing postprandial lipoproteins. A simpler choice may be the use of non-HDL-cholesterol (Non-HDL-c = *Total cholesterol minus HDL cholesterol* *This measures LDL-c + cholesterol associated with triglycerides*¹.) This is accurate and reliable in a non-fasting state, and would be simple to incorporate into clinical practice.

“In the end, is it the triglyceride levels or the associated changes in metabolism that explain the high risk associated with postprandial triglyceride levels?” In clinical practice the argument may be as academic as the debate about which came first, the chicken or the egg.

It is important to aggressively and comprehensively treat patients with dyslipidemias that include high levels of TG, low levels of HDL-c, and the presence of small LDL-c particles, using both lifestyle and medications.²

JAMA July 18, 2007; 298: 336-38 Editorial by Patrick E McBride, University of Wisconsin School of Medicine and Public Health, Madison

1 The National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) recommend use of non-HDL-c for risk assessment, and as a secondary therapeutic goal when the TG is 200 to 500 mg//dL

2 Statins, gemfibrozil and niacin, alone or in combination, reduce TG levels.

A Bite A Day Keeps The Doctor Away

7-8 EFFECTS OF LOW HABITUAL COCOA INTAKE ON BLOOD PRESSURE AND BIOACTIVE NITRIC OXIDE.

Apart from fruits and vegetables, cocoa products contribute a major proportion of total phenol intake. They are not included in current treatment advice.

Cocoa is especially rich in flavanols (a subclass of polyphenols) that have been suggested to mediate the favorable effects of cocoa products on cardiovascular health and BP. The effects of cocoa flavanols may be due to enhancement of endothelial nitric oxide, thereby lowering BP.

This study determined the effects of low doses of polyphenol-rich dark chocolate on BP.

Conclusion: Inclusion of small amounts of dark chocolate as part of the diet reduced BP.

STUDY:

1. Randomized, parallel-group trial followed 44 adults (mean age 64), for 18 weeks.
2. Subjects were volunteers from the community. All were in good health. None were taking antihypertension medication. All had either pre-hypertension (BP 130/85 to 139/89), or grade 1 hypertension (BP 140/90 to 160/100). Mean BP = 147/87. None had BP more than 170/100.
3. Randomized to: 1) 6 grams dark chocolate (one piece of a 16-piece bar of 100 grams commercially available chocolate) containing 30 mg of polyphenols, or 2) 6 grams of polyphenol-free white chocolate.¹ Both contained 30 kcal and similar macronutrients and electrolytes. (Eg, sodium 4 mg; potassium 16 mg.)
4. Participants were instructed to ingest the chocolate between 8 PM and 10 PM. (A piece placed on the pillow?)
5. Main outcome = change in BP at 18 weeks.

RESULTS

1. Change (mean) in BP baseline to 18 weeks:

Dark chocolate	White chocolate
- 2.9/1.9 (CI = 1.6/1.0)	No change

(BP was lowered progressively over the 18 weeks.)
2. Hypertension prevalence declined from 86% to 68% in the dark chocolate group. BP reductions were more pronounced in hypertensive as compared with normotensive participants.
3. In the dark chocolate group, the BP decrease was accompanied by a sustained increase in serum 5-nitrosoglutathione by 0.23 nmol/L. And the appearance of cocoa phenols in the plasma.
4. No change in weight, lipids, or glucose
5. No adverse events.

DISCUSSION

1. "We demonstrated that intake of low habitual amounts of dark chocolate caused progressive reductions in systolic and diastolic BP in older subjects with pre-hypertension or stage 1 hypertension."
2. The decrease in BP was associated with an increase in circulating levels of vasodilating 5-nitrosoglutathione, suggesting a causative role on BP regulation.
3. Although the effects on BP were small, they are clinically noteworthy. On a population basis, it has been

estimated that a 3-mm reduction in systolic would reduce the relative risk of stroke mortality by 8%, of coronary artery disease mortality by 5%, and of all-cause mortality by 4%.

4. A plausible mechanism: 5-nitrosoglutathione in dark chocolate results in increases in the production of nitric oxide, a strong vasodilator.
5. The similar amount of BP reduction in this study, compared with other studies using much larger chocolate doses over shorter times suggests that the cumulative phenol dose over time may determine the magnitude of transcriptional endothelial nitric oxide synthase activity and thus sustained BP reduction.
6. “The most intriguing finding of this study is that small amounts of commercial cocoa confectionary convey the similar BP-lowering potential compared with conventional dietary modifications that have proven efficacy to reduce cardiovascular event rate.”
7. “Adoption of small amounts of flavanol-rich cocoa is a dietary modification that is easy to adhere to and therefore may be a promising behavioral approach to lower blood pressure in individuals with above-optimal blood pressure.”
8. Any benefits in reductions of cardiovascular endpoints resulting from dark chocolate are speculative at this time.

JAMA July 4, 2007; 298: 49-60 Original investigation, first author Dirk Taubert, University Hospital of Cologne, Germany, which funded the study.

1 Chocolate bars were obtained from companies in Germany

I mentioned the data on 5-nitrosoglutathione and phenols for the benefit of those more familiar with these compounds than I am. RTJ

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Can Reduce Recurrence. Little Impact On Prevalence

7-9 SURGERY + COMPRESSION VS COMPRESSION-ALONE FOR VENOUS LEG ULCERS

An estimated 5% of the world’s population has venous disease in the legs; 1% has venous ulcers at some time in their lives. Venous leg ulcers impair quality-of-life and are difficult to treat.

These ulcers are caused by sustained high venous pressures due to venous disease, obesity, immobility associated with arthritis, or even old age itself. Superficial venous incompetence, the usual cause of varicose veins, can be detected in most patients with venous ulcers.

Compression using four layer bandaging is the mainstay of treatment. It completely heals ulcers in a mean of 8 weeks when delivered by trained nurses in the community. The efficacy of bandaging is not influenced by the underlying venous abnormality.

A report of long-term results of a study comparing compression alone vs compression + superficial surgery in patients with open, or recently healed leg ulcers, and superficial venous incompetence appeared in the BMJ this week.¹ Ulcer healing, ulcer recurrence, and ulcer-free time were recorded over 4 years.

(Most previous trials either ignored the role of compression therapy, or compared surgery with compression, which is inappropriate as both are effective treatments that should be complementary.)

The study clarifies the role of superficial venous surgery in people willing and able to have an operation.

There was no significant difference between compression-alone, and surgery + compression on ulcer healing at 3 years. Recurrence, which otherwise happens in a quarter of patients each year was almost halved by surgery. The benefit was most obvious in patients who had incompetence affecting only the superficial veins or those with “segmental” deep venous incompetence, in which reflux is found in limited segments of deep veins without widespread valve failure. (Valve failure is largely confined to the superficial veins.) Ablating incompetent superficial veins improves deep venous function.

Sadly, these encouraging results will have little influence on overall ulcer prevalence. Many elderly people in the community refuse to attend hospitals for either venous investigations or surgery.

Simple pinch grafting is an exception; it can be done in the community under local anesthesia, and speeds the healing of large ulcers.

Patients should be checked for arterial disease before four layer bandaging

There is no need to delay venous surgery when appropriate for uninfected ulcers.

Both superficial venous surgery and compression will almost certainly have a role in ulcer prophylaxis.

Conclusion: Surgical correction of superficial venous reflux in addition to compression bandaging did not improve ulcer healing, but reduced the recurrences of ulcers.

BMJ July 14, 2007; 335: 55-56 Editorial by Charles N McCollum, University Hospital of South Manchester, UK
1 “Long-Term Results Of Compression Therapy Alone Versus Compression Plus Surgery In Chronic Venous Ulceration (ESCHAR)”, first author Manjit S Gohel, Cheltenham General Hospital, Gloucester, UK

Impaired Reading Fluency, Has A Strong, Independent Association With Death.

7-10 HEALTH LITERACY AND MORTALITY AMONG ELDERLY PERSONS

Education, as measured by the number of years of school completed, is a predictor of mortality. One study reported that, in the USA, persons without a high school education lost about 9 more potential life-years compared with those completing high school. Many factors may explain the differences associated with education: job opportunities, annual income, better housing, more nutritious foods, and health insurance.

Individuals with low levels of health literacy have less health knowledge, worse self-management of chronic disease, lower use of preventive services, and worse health.

This study asks: Could reading fluency have a direct effect on health?

Conclusion: Inadequate health literacy, as measured by reading fluency, predicted mortality.

STUDY

1. Prospective cohort study followed over 3200 community-dwelling Medicare enrollees (mean age = 74) in 4 US centers.
2. Interviewed subjects in 1997 to determine their demographic characteristics, chronic conditions, self-reported physical and mental health, and health behaviors.
3. Measured health literacy by testing for reading fluency (Test of Functional Health Literacy in Adults). Scores range from 0 to 100. Scores of 0 to 55 indicate inadequate literacy. Individuals with impaired health literacy often misread the simplest materials, including prescription labels, and appointment slips. Scores of 56 to 66 indicate marginal literacy. Scores of 67 to 100 indicate adequate health literacy. The latter will successfully complete most of the reading tasks required to function in the healthcare setting, but may still misread the most difficult numerical information.
3. Main outcome = all cause mortality according to the National Death Index through 2003.

RESULTS

1. A total of 815 participants died during an average follow-up of 68 months.
2. Crude mortality rates according to health literacy:

Adequate (n = 2094; 64%)	Marginal (n= 366; 11%)	Inadequate (n = 800; 24%)
19%	29%	39%
3. Hazard ratios for all-cause mortality after adjustment for several possible confounders:

1.00	1.13	1.52
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4. In contrast, years of school completed were only weakly associated with mortality.
5. Participants with inadequate health literacy had higher rates of cardiovascular death, but not of death due to cancer.
6. Participants with inadequate health literacy were more likely to be non-white, to have less annual income and education, and to be in worse physical and mental health.
7. Interestingly, those with inadequate health literacy were *less* likely to have ever smoked cigarettes, and to have used alcohol during the preceding month. They were less likely to perform frequent vigorous exercise, and more likely to have body mass index under 18.5

DISCUSSION

1. Inadequate health literacy, as measured by reading fluency, had a strong, independent association with death. The magnitude of the association was similar to the association between low annual income and mortality.
2. In 2003 a National Assessment of Adult Literacy survey reported that over 75 million adults in the USA had only basic, or less than basic, health literacy.
3. Individuals with more education and higher levels of health literacy, have a better capacity to obtain, process, and understand basic health information, and to obtain services needed to make appropriate health decisions.

4. Years of school completed was weakly associated with mortality. This is an inaccurate measure of true educational attainment. Many individuals progress through the educational system without meeting desired goals, including the ability to read at grade level. Among older persons, years of school completed is problematic because it does not capture life-long learning.

4. Possible explanations for the association:

Inadequate health literacy is associated with less knowledge of chronic diseases and worse self-management.

It is related to lower knowledge of medications and dosing instructions and poorer adherence to the medication regimen.

Screening and immunizations are lower.

5. Widespread improvements in health and health care communication will likely be necessary to reduce the association between health literacy and mortality.

CONCLUSION

Inadequate health literacy, as measured by reading fluency, independently predicted death among community-dwelling elderly persons.

Reading fluency was a more powerful variable than education for examining the association between socioeconomic status and health.

Archives Int Med July 23, 2007; 167: 1503-09 Original investigation, first author David W Baker, Feinberg School of Medicine, Northwestern University, Chicago, IL

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From 1 in 143 To 1 in 1361

7-11 ESTIMATING RISK OF CANCER ASSOCIATED WITH RADIATION EXPOSURE FROM 64-SLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

Computed tomography coronary angiography (CTCA) has become a common diagnostic test.

Coronary angiography is the gold standard for diagnosis of coronary artery diseases (CAD). It is associated with costs and morbidity (~ a 2% rate of complications).

CTCA (64-slice) visualizes the coronary arteries with spatial resolution as low as 0.4 mm. Sensitivity and specificity of this test is high. Negative predictive value is greater than 95%. CTCA may emerge as the diagnostic test of choice for patients with intermediate pre-test probability of CAD. One setting in which CTCA has been proposed as particularly useful is in the rapid evaluation (less than 20 minutes) of emergency department patients with chest pain. Millions of patients with chest pain are evaluated each year in EDs. Up to 25 % are ultimately diagnosed with acute coronary syndrome; up to 72% are admitted to the hospital for further observation.

It is generally perceived that a cancer risk is associated with CTCA. Few quantitative data are available. A FDA report suggested an increased risk of fatal cancer of 1 in 2000.

The recent report of the Biological Effects of Ionizing Radiation (**BEIR**) provides a framework for estimating cancer risk. It incorporates data from atomic bomb survivors as well as from medical and occupational radiation studies. The data supports the so-called linear, no threshold risk model for low dose exposures to X-rays. (I.e, risk of cancer proceeds in a linear fashion with no lower threshold.)

This study estimated the lifetime attributable risk of cancer incidence associated with radiation exposure from a single 64-slice CTCA study.

Conclusion: A single CTCA is associated with a detectable increase in risk of future cancer.

STUDY

1. Estimated organ doses from a standard 64-slice spiral CTCA to standardized male and female patients.
2. Using standard spiral CT protocols estimated age and sex specific lifetime-attributable risk of cancers using the BEIR approach.
3. Main outcome = whole body and organ lifetime attributable risks of cancer incidence.

RESULTS

1. Lifetime cancer risk from CTCA varied from 1 in 143 for a 20-year old woman to 1 in 1361 for an 80-year-old man.
2. When heart and aortic scans were combined, risk increased.
3. The highest lifetime attributable risks were for lung cancer and, in younger women, for breast cancer.

DISCUSSION

1. There was a marked variation in cancer risk by age, sex, and scan protocol. Rather than a relatively constant cancer risk of 1 in 1000 or 1 in 2000, the lifetime attributable risk ranged from 1 in 5000 for an 80-year old man to nearly 1 in 100 for 20-year old women.
2. Radiosensitivity of many organs (including the breast) decline with age. And older patients are less likely to survive long enough to develop the radiation-induced cancers.
3. A long lag-time is typical from acute radiation exposure to the development of malignancy. A 12-year minimum latency from radiation exposure to excess breast cancer risk has been described in Japanese atomic bomb survivors.
4. Women have greater radio-sensitivities and risks of cancers than men. Their breasts are in the field of radiation from CTCA.
5. "The risks reported here provide practitioners with data that can be used to assess the risk vs benefit of CTCA in specific patients."
6. "This study provides a simplified approach, albeit one that we believe is the best available from current data."

7. The results of this study suggest that CTCA should be used with particular caution in the evaluation of young individuals, especially women. Coronary angiography is also related to immediate and even more frequent major complications. (*Ie, clinicians and radiologists should decide the benefit / harm-cost ratio of standard angiography vs CTCA for individual patients.*)
8. These lifetime-attributable risks are calculated from exposure to one CTCA. Risks from radiation are cumulative over a lifetime.

CONCLUSION

The estimated lifetime attributable risk of CTCA varies widely depending on age, sex, and protocol. However, risks of cancer due to radiation are not negligible.

JAMA July 18, 2007; 298: 317-23 Original investigation, first author Andrew J Einstein, Columbia University College of Physician and Surgeons, New York.

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