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FOR

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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

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* MAY 2007

"Sodium is necessary, but not sufficient"

5-1 SODIUM AND POTASSIUM IN THE PATHOGENESIS OF HYPERTENSION

Primary hypertension results from the interplay of internal derangements (primarily in the kidney), and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor. Numerous studies have shown the adverse effect of a surfeit of sodium on arterial pressure.

By contrast, potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

This review examines how the interdependency of sodium and potassium influences blood pressure (BP). Sodium and potassium act together to influence BP. Excess sodium and a deficit of potassium are the dominant environmental factors in the pathogenesis of primary hypertension.

"Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol/day." (~ 3 grams of NaCl). "It appears, then, that sodium intake that exceeds 50 to 100 mmol per day (3 to 6 grams of NaCl) is necessary, but not sufficient for the development of primary hypertension."

Isolated populations that eat natural foods (in which hypertension affects less than 1% of people) have an individual potassium intake that exceeds about 6 grams a day, and a sodium intake of only 0.5 to 1.0 grams—a ratio greater than 3/1 and closer to 10/1). People in industrialized countries (in which hypertension affects about one third of the population) ingest 1.2 to 2.7 grams of potassium, and as much as 2.3 to 9.2 grams of sodium.

Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake. Population studies have shown an inverse relation between potassium intake and BP, the prevalence of hypertension, and the risk of stroke.

A modified diet that approaches the high potassium:sodium ratio of the diets of our human ancestors is a critical strategy for the primary prevention and treatment of hypertension.

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The article goes into much more detail. I believe it should be required reading for all primary care clinicians. It may also motivate patients to be more concerned about their diet.

Primary hypertension is no longer "essential" or idiopathic It is a disease of civilization.

The taste for salt is acquired. People who are reared on a low salt diet, when moving to a population with high salt intakes will complain that the food is too salty.

Unfortunately, fruit and vegetables are often more costly than most other foods.

A Low-Glycemic Load Diet Promotes More Weight Loss In Patients With A High Insulin-Response To Glucose.

5-2 EFFECTS OF LOW-GLYCEMIC LOAD VS LOW-FAT DIET IN OBESE YOUNG ADULTS

Some individuals have a higher insulin response to glucose ingestion. They may be more likely to develop postprandial hypoglycemia.

This randomized trial enrolled 73 obese young adults (mostly female; age range 18-35; mean = 27) for

18 months. All had a BMI of 30 and above. Prior to randomization, a 75-g glucose tolerance test determined serum insulin levels at 30 minutes. The median serum insulin concentration at this time was 58 micro-IU/mL.

Subjects were randomized to: 1) Low-glycemic load diet: 40% of energy from carbohydrate (emphasizing low glycemic index foods); 35% from fat; and 25% from protein, or 2) Low-fat diet: 20% of energy from fat; 55% from carbohydrate; and 25% from protein. The diets were ad lib. No calorie counting or limitation on the quantity of food intake was involved. Intake was determined by the subjects' feeling of satiety.

Results at 18 months:

1) Subjects with baseline insulin concentrations greater than 58 micro-IU/mL:

Individuals on the low glycemic load diet lost 5.8 kg

Individuals on the low fat diet lost 1.2 kg

2) Subjects with baseline insulin concentrations below 58 micro-IU/mL.

Individuals on a low glycemic load diet lost about 2 kg

Individuals on a low fat diet also lost about 2 kg.

(Ie, insulin concentration was an effect moderator for weight loss.)

Conclusion: For obese individuals with high insulin concentrations after a glucose load, a low-glycemic diet may promote more weight loss than a low-fat diet.

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If you are a "high insulin responder" then changing your diet to a low glycemic load diet would lower the resultant post-prandial blood glucose elevation, and lower the insulin response. This would in turn result in the 2-hour post-meal blood glucose being higher than at baseline. Post-prandial hypoglycemia would be less likely to occur; hunger would not be as acute; and caloric intake would likely be less. Weight loss would be more likely to be greater than with a low fat, higher carbohydrate diet.

5-3 OSTEOPENIA

Bone mineral density (**BMD**; expressed as grams per square centimeter) is a better predictor of fracture than BP is of stroke. The relative risk of hip fracture is 2.6 for each 1 standard deviation (**SD**) decrease in BMD at the hip. The risk of fracture is continuous, with no absolute cutoff value to define a pathological state.

The WHO has defined osteopenia and osteoporosis based on "T-scores". (*Standard deviations of bone mineral density from the mean of young persons. See the full abstract.)*

An estimated 33 million Americans (the great majority, women) have osteopenia. Osteopenia is analogous to pre-hypertension, impaired fasting glucose, and borderline high cholesterol in defining an intermediate-risk group with somewhat uncertain boundaries.

Although the risk of fragility (low trauma) fracture is greater among individuals with osteoporosis than among those with osteopenia, the numbers of individuals in the population who have osteopenia is far greater than those with osteoporosis. (39% vs 6% in primary care practice.) The frequency of fragility fractures overall is greater in persons with osteopenia than with osteoporosis. The lifetime risk of fragility fracture is 40% in women and 13% in men. Because osteopenia is much more common than osteoporosis, the majority of fractures occur in patients with osteopenia.

Measurements of bone mineral density alone cannot effectively discriminate between patients with osteopenia who will have fractures, and those who will not have a fracture.

A clinical dilemma posed by osteopenia arises when BMD in the osteopenic range is identified in patients without an obvious indication for drug treatment (such as a fragility fracture). There are risk factors other than BMD which identify patients with osteopenia who are at increased risk for fracture as compared with others with similar values for BMD. (*See the full abstract.)*

"Clinical risk factors should be considered in combination with measurement of bone mineral density to estimate fracture risk and guide investigation." The patient's own valuation of risks and benefits should influence the choice between lifestyle treatment alone or lifestyle + drug therapy.

"Unless the patient strongly prefers to take anti-resorptive medication, or has a T-score near the osteoporotic range with several risk factors for fracture, encouragement of lifestyle modifications with reassessment in 2 to 3 years is a reasonable strategy, and is our recommendation for the majority of patients with osteopenia."

Prevention of osteoporosis with drug therapy implies a beginning of therapy before osteoporosis develops. That is, either when the patient has a normal bone mineral density, or is osteopenic. Drug treatment is recommended for patents with osteoporosis. Recommendations about treatment for patients with osteopenia vary. I would err on the side of beginning drug treatment at an earlier stage and at an earlier age.

At present, drugs are considered for prevention of further bone loss (secondary treatment), not for primary prevention of osteopenia and osteoporosis.

I believe that any disabling disease with a lifetime risk of 40% should be prevented. We should not wait until it is established to treat. We do not wait for stroke to treat hypertension. We do not wait for a myocardial infarction before treatment of dyslipidemia. Anyone living in a retirement complex as I do will see their friends (both male and female) develop disabling kyphosis and hip fractures. I believe many of these could be prevented by interventions started at an earlier stage and at an earlier age than now is recommended. Why not a "polypill" (combined vitamin D + calcium + low dose bisphosphonate) to be taken regularly, beginning at age 50, to prevent bone loss much as a "polypill" is recommended by some authorities for universal prevention of cardiovascular disease.

I certainly would welcome such a long-range study.

Optimum intake of Vitamin D and calcium should be established at all ages, including the young. This may require lifelong supplements.

5-4 IRRITABLE BOWEL SYNDROME: Clinical Update

A concise review.

Thirteen clinical points from the Rome criteria to drug treatment

Read the full abstract.

Should Not Be Greater Than 75 or 81 Mg/Day.

5-5 ASPIRIN DOSE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

This systematic review analyzed 11 studies of aspirin therapy for CVD.

A. Therapy requiring an immediate effect (eg, acute myocardial infarction, TIA, stroke):

Aspirin taken orally is rapidly absorbed. Peak plasma levels are achieved rapidly (30 minutes).

A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to achieve maximal antiplatelet activity. Absorption and onset of antiplatelet activity are shortened by chewing the tablet or drinking a solution (eg, *Alka-Seltzer*). Maximum inhibition of thromboxane production is achieved in 20 to 30 minutes compared with swallowing a whole aspirin tablet (60 minutes). To rapidly achieve maximal antiplatelet activity of aspirin at least 163 mg should be chewed or dissolved and then swallowed.

B. Long-term therapy:

Aspirin irreversibly inactivates platelet COX-1. De-novo synthesis of new COX-1 by platelets is minimal. The long-term effects of aspirin on platelets are cumulative.

Once complete inactivation of platelet COX-1 is achieved, minimal doses of aspirin are required to ensure adequate acetylation of COX-1 and inactivation of thromboxane production. New platelets containing the normal amounts of COX-1 are formed at a rate of 10% daily. As little as 30 mg of aspirin daily is required to completely inhibit thromboxane production in healthy individuals. In patients with chronic stable angina, thromboxane synthesis is chronically elevated and 50 mg of aspirin daily may be needed.

A number of trials and meta-analyses have evaluated the optimal aspirin dose in various clinical settings. “The one nearly constant finding among all of these studies has been the lack of a relationship between increasing aspirin dosage and improved efficacy. In fact, the trend in benefit has almost uniformly favored lower dosages.”

The 11 trials reviewed by this study included nearly 10 000 patients with atherosclerotic disease receiving doses of 30 to 1300 mg per day). A significant benefit of higher doses was not demonstrated in any trial. In most trials, the lowest event rates were realized among patients randomized to the low-dose groups.

The major risk of aspirin (as with other NSAIDs) is bleeding—the majority from the g.i. tract. Although this increase is more commonly attributed to non-aspirin NSAIDs, a recent evaluation of patients hospitalized for ulcer bleeding found that aspirin was responsible for as much ulcer bleeding as all other NSAIDs combined. Low-dose aspirin was one of the most common causal agents.

Aspirin inhibits COX-1 in the gastric mucosa (as well as in platelets) and decreases the production of prostaglandins which protect the gastric mucosa. The influence of aspirin on gastric prostaglandins is dose-dependent. Almost 50% inhibition occurs at 30 mg / day—maximal inhibition at 1300 mg / day. “All conventional doses of aspirin are associated with increased bleeding risk.” But, a relationship between higher aspirin dose and increased risk of bleeding has been demonstrated in clinical trials. A UK trial found almost double the risk among patients randomized to 1200 mg/day compared with 300 mg/day. A Dutch trial found a trend toward less bleeding in the group receiving 30 mg/day compared with 283 mg/day. However, not all pooled study analyses have come to the same conclusion.

Considering that 50 million Americans are taking daily aspirin, if there is a difference in risk of major g.i. bleeding between 30 mg and 325 mg, then the larger dose would lead to an excess of 900 000 major bleeding events per year.

An association between increases in aspirin dose and adverse effects has been confirmed. No such dose relationship has been identified for efficacy.

Conclusion: Currently available clinical data do not support the routine, long term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher doses are associated with increased risks of gastrointestinal bleeding.

Effective Prophylaxis. Not Effective Treatment

5-6 QUADRIVALENT VACCINE AGAINST HUMAN PAPILLOMAVIRUS TO PREVENT HIGH-GRADE CERVICAL LESIONS

Multicenter, multicountry randomized, double-blind trial assigned over 12 000 women between ages 15 and 26 (mean = 20) to: 1) Three doses of the vaccine, or 2) Placebo injections. Injections were given at day 1, month 2, and month 6.

Efficacy was almost 100% in the susceptible population (n = 10 565). Only one vaccinated individual without HPV infection at baseline (determined by PCR or serology) developed cervical intraepithelial neoplasia (CIN-3) This single subject was positive for HPV-52 at baseline.

Vaccination was *not* effective in those who were positive for HPV-16 or 18 at baseline. (n = 782) In this group there were 98 cases of CIN-2 or 3, and 5 cases of adenocarcinoma in situ—most due to HPV-16.

Conclusion: In young women who had *not* previously been infected with HPV-16 or HPV-18, vaccination lowered the occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18. Widespread immunization of female children and adolescents may result in substantial decrease in HPV-16 or HPV-18 related cervical disease, including cervical cancer.

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Recently there has been some discussion of mandatory immunization of young girls before onset of sexual activity. Enthusiasm for this is waning.

"Most Cases Are Unrecognized"

5-7 COELIAC DISEASE IN PRIMARY CARE

Celiac disease (**CD**) is characterized by a life-long intolerance to certain proteins (known collectively as gluten) contained in wheat, rye, and barley. It is an unusual combination of food intolerance and auto-immunity. The resultant chronic inflammation of the proximal small intestine results in atrophy of villi, and abnormal intestinal permeability with impaired absorption of nutrients and increased secretion of solids.

CD affects about 1% of the general population. Most cases are unrecognized. Diagnosis is often delayed. "This is surprising, given how common the disease is, and how seriously its effects can be." It may be because most patients with CD do not have typical symptoms of malabsorption. Even if these symptoms are present, their non-specific nature may not trigger diagnostic suspicion of the disease.

The gold standard for the diagnosis of CD is a positive duodenal biopsy.

In primary care, the American Gastroenterology Association recommends the use of antibody to trans-glutaminase as the single diagnostic serological test. But, positive results are not sufficient to diagnose CD. Biopsy is still essential, especially if the patient is to be placed on a life-long gluten-free diet.

A gluten-free diet corrects anemia, and restores normal nutritional and biochemical status. It substantially improves quality of life, particularly if troublesome gastrointestinal symptoms have been present.

This issue of BMJ reports a validated clinical prediction rule to determine all cases of celiac disease in people referred for gastroscopy.:

All received 1) test for antibody to transglutaminase, and 2) duodenal biopsy.

A. They classified patients as being at

1) "High risk" for CD. (N = 739 with diarrhea, weight loss, and/or anemia), or

2) "Low risk" (N = 1261. All other patients with indications for gastroscopy: abdominal pain; reflux; dyspepsia; nausea and vomiting, and chest pain. Ie, not suggestive of CD.)

B. Results;

1) High risk patients (n = 739)

Antibody to transglutaminase positive (n = 154; CD diagnosed by biopsy in 64 [40%])

Antibody to transglutaminase negative (n = 585 CD diagnosed by biopsy in 7 [1.2%])

2) Low risk patients (n = 1161)

Antibody to transglutaminase positive (n = 91; CD diagnosed by biopsy in 6 [7%])

Antibody to transglutaminase negative (n = 1170; CD diagnosed by biopsy in none [0%])

. The investigators developed a prediction rule:

All patients with a clinically "high risk" should be biopsied.

All patients with a positive antibody to transglutaminase should be biopsied.

Patients at "low risk" of CD, and a negative antibody test do not require biopsy.

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CD is a mimic. Primary care clinicians should put it on top of their "Am I missing something" list. Diagnosis may prevent years of disability and even death.

Some primary care clinicians may wish to recommend a gluten-free diet for a few weeks as a therapeutic test.

Prognosis Is Better With Ruptured Disk Than With Spinal Stenosis.

5-8 BACK SURGERY—WHO NEEDS IT?

Two studies in this issue of NEJM help define the type of patients who may benefit from surgery.

The first study randomized patients with severe sciatica due to herniated disks. None had resolution of pain within 6 to 12 weeks of conservative treatment. Patients were randomized to 1) early diskectomy, or 2) continued non-surgical therapy, or delayed surgery.

Reserving surgery for patients whose pain did not sufficiently improve for 6 to 12 weeks of non-surgical treatment is important because, even without surgery, sciatica improves within 3 months in 75% of patients.

Even among patients with persistent sciatica, recovery was likely whether or not surgery was performed. Most herniated disks shrink over time. But surgery accelerates the pace of recovery, and for some patients faster recovery may be worth the risks.

After a year, however, recovery was about the same with non-surgery as with surgery (95% in both groups), although almost 40% of patients initially assigned to the non-surgical group crossed-over to surgery.

The second study addressed degenerative spodylolisthesis with associated spinal stenosis. This condition causes both back and leg pain. The study was randomized, but there were so many unintended crossovers from the non-surgical group to the surgical group that the authors highlighted their analysis according to treatment received rather than intention-to-treat, essentially creating a single large cohort study. *(Indicating that many patients perceived a high degree of pain and disability.)*

About 95% of surgical patients underwent a spinal fusion procedure. Thus, the study was essentially a trial of fusion for spodylolisthesis. Fusion surgery is more invasive than diskectomy, with higher complication rates.

The study reported that surgery offered a significant advantage over non-surgical therapy. “The study further solidifies the basis of performing spinal fusion in patients with persistent leg pain, spodylolisthesis, and associated spinal stenosis.”

At 2 years, treatment outcomes were determined in 511 patients. In all outcomes, including improvement in pain and functioning, surgery was superior to non-surgical care.

Patients’ ratings surgery vs no-surgery:

Very or somewhat satisfied with symptoms 69% vs 32%

Self-rated major improvement 74% vs 24%

Although surgery often relieved symptoms, many were not satisfied with the results of their surgery. Prognosis is not as good as with ruptured disks. RTJ)

Modest Exercise For Little Over An Hour A Week Had A Training Effect.

5-9 EFFECTS OF DIFFERENT DOSES OF PHYSICAL ACTIVITY ON CARDIORESPIRATORY FITNESS AMONG SEDENTARY, OVERWEIGHT OR OBESE POSTMENOPAUSAL WOMEN WITH ELEVATED BLOOD PRESSURE

Cardiovascular disease is the primary cause of death in postmenopausal women (30% of these women report no physical activity at all). The presence of inactivity increases with age. Fitness declines at 1% to 2% per year during the postmenopausal years. Physiological changes associated with aging may decrease the body’s ability to maintain or improve fitness.

This trial examined the effect of 50%, 100%, and 150% of the NIH physical activity recommendations on cardio-respiratory fitness in sedentary, overweight or obese, postmenopausal women with elevated BP.

Randomized, dose-response exercise trial entered 464 volunteer postmenopausal women (age 45 to 75; mean = 57). None had a history of cardiovascular disease or any other serious medical condition. All were sedentary (not exercising over 20 minutes on more than 3 days per week and taking less than

8000 steps/day assessed by pedometer). All were overweight or obese (mean BMI = 32); mean BP = 140/81.

Randomized to:

1) Non-exercise group asked to maintain their usual daily activity.

2) Exercise groups:

4 kcal/kg/wk. (50% of recommended exercise level)

8 kcal/kg/wk. (100% of recommended exercise level)

12 kcal/kg/wk. (150% of the recommended exercise level)

All exercise groups continued to participate in the laboratory supervised exercise sessions 3 or 4 times a week for 6 months. All participants continued their usual activities (except for the training periods) during the week.

Mean minutes of exercise per week: 4 kcal/kg/week = 72; 8 kcal/kg/week = 139; 12 kcal/kg/week = 192.

At 6 months, the exercise groups increased their absolute VO2 compared with the no-exercise group: 4 kcal/kg/week +4.2%; 8 kcal/kg/week +6.0%; 12 kcal/kg/week +8.2% (a training effect).

The primary finding of the trial: A controlled exercise program in postmenopausal women resulted in a dose-response increase in fitness. Women who exercised 3 or 4 times a week increased their fitness in proportion to the amount of energy expended during the exercise sessions.

"Perhaps the most striking finding of our study is that even activity at the 4-kcal/kg/week level (approximately 72 minutes pre week) was associated with a significant improvement in fitness compared with women in the non-exercise group."

Conclusion: Previously sedentary, overweight, or obese postmenopausal women experienced a graded dose-response in fitness across levels of exercise training. Even modest exercise for little over an hour a week had a training effect.

Surgery Should Not Be Performed If Systematic Follow-Up Is Not Available

5-10 BARIATRIC SURGERY FOR MORBID OBESITY

Bariatric surgery reduces caloric intake by modifying the anatomy of the g.i. tract. Operations are classified as restrictive or malabsorptive. The changing popularity of specific surgical procedures over time suggests that the ideal procedure has not been established. Laparoscopic procedures are available.

Conditions associated with obesity consistently improve after surgery. (Eg, 77% of patients with type 2 diabetes no longer required medications after surgery.)

Thorough medical evaluation is required prior to surgery. The psychological evaluation of candidates for surgery is one of the most important and difficult elements of the clinical assessment. Most patients presenting for surgery have one or more psychiatric disorders.

Patients undergoing surgery often believe they will lose more weight than is consistent with clinical experience. And may think that minimal personal effort or risk is involved.

Perioperative care requires specialized expertise and facilities. Choosing surgeons and hospitals that have great experience is essential.

A comprehensive plan for long-term care is necessary. Surgery should not be performed if systematic follow-up is not available, and should not be planned until the patient has made a commitment to participate in such care.

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Surgical treatment is complex—not to be undertaken lightly. Reading the original article may be helpful to patients with morbid obesity who are considering surgery.

Bariatric surgery is the only effective treatment for morbid obesity.

5-11 ONCE-YEARLY ZOLEDRONIC ACID FOR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

A single *intravenous* infusion of zoledronic acid (**ZA**; a bisphosphonate) decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis.

This study assessed the effects of annual infusions of ZA on fracture risk over a 3-year period.

Randomized, double-blind, placebo-controlled trial entered over 3800 postmenopausal patients (mean age = 73). All had a bone mineral density T-score of -2.5 or less (*osteoporosis*) at the femoral neck, with or without existing vertebral fracture, or a T-score of – 1.5 or less (*osteopenia*) with evidence of at least 2 mild vertebral fractures or one moderate vertebral fracture.

Randomized to: 1) ZA (5 mg) given i.v. as a single dose over 15 min, or 2) Placebo i.v. Both were given at baseline, at 1, and at 2 years. In addition, all patients received oral daily calcium (1000 to 1500 mg), and vitamin D (400 to 1200 IU).

Treatment with ZA reduced the risk of fracture during 3 years

	ZA	Placebo	Absolute difference	NNT*
Vertebral fracture	3.3%	10.9%	7.6%	14
Hip fracture	1.4%	2.5%	1.1%	91

Adverse effects: Post-dose symptoms occurred more commonly in the ZA group than in the placebo group: transient slight increase in serum creatinine, chills, fever, myalgia, flu-like symptoms, headache, arthralgia, nausea, bone pain, back pain. (6% for placebo vs 16% for ZA.) Atrial fibrillation (0.5% for placebo vs 1.3% for ZA.)

Conclusion: A once-yearly infusion of ZA during a 3-year period was associated with a sustained reduction in risk of fractures. “In addition, the treatment had a favorable safety profile and was generally well tolerated.”

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The study was not a direct comparison The proper protocol to determine efficacy and safety of a new drug is to compare it with an effective, established drug if one is available, and not with a placebo. Drug vs placebo is no longer a valid comparison when an effective established drug is available.

I would not prescribe or advise ZA for my patients should it become generally available. Much longer observations must be in place to assess safety to convince me that it is preferable.

ABSTRACTS MAY 2007

"Sodium is necessary, but not sufficient"

5-1 SODIUM AND POTASSIUM IN THE PATHOGENESIS OF HYPERTENSION

Hypertension is "responsible for most deaths worldwide". Primary hypertension (also known as essential or idiopathic hypertension) accounts for as many as 95% of all cases.

Primary hypertension results from the interplay of internal derangements (primarily in the kidney), and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor. Numerous studies have shown the adverse effect of a surfeit of sodium on arterial pressure.

By contrast, potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

This review examines how the interdependency of sodium and potassium influences blood pressure (BP). Sodium and potassium act together to influence BP. Excess sodium and a deficit of potassium are the dominant environmental factors in the pathogenesis of primary hypertension.

Dietary Sodium and Hypertension:

"Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium is less than 50 mmol per day." *(~ 3 grams of NaCl*) "These conditions are observed mainly in populations in which people consume more than 100 mmol of sodium chloride per day." (Over 6 grams of salt per day)

The median urinary NaCl in 32 countries reported by the INTERSALT was about 10 grams per day. But, most people remain normotensive. "It appears, then, that sodium intake that exceeds 50 to 100 mmol per day (*3 to 6 grams of NaCl)* is necessary, but not sufficient for the development of primary hypertension."

In the Dietary Approaches to Stop Hypertension (DASH) study, a reduction in sodium intake caused stepwise decreases in BP.

Potassium Content of Sodium-Rich Diets:

As compared with diets based on natural foods, diets based on processed foods are high in sodium and low in potassium. (Eg, a cup of canned chicken noodle soup contains about 2.8 grams of NaCl, and 0.3 grams of potassium. An orange contains no sodium and 0.39 grams of potassium.)

Isolated populations that eat natural foods (in which hypertension affects less than 1% of people) have an individual potassium intake that exceeds about 6 grams a day, and a sodium intake of only 0.5 to 1.0 grams—a ratio greater than 3/1 and closer to 10/1). People in industrialized countries (in which hypertension affects about one third of the population) ingest 1.2 to 2.7 grams of potassium, and as much as 2.3 to 9.2 grams of sodium.

Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake.

Movement of isolated populations into more urban areas (from high K:Na ratio to high Na:K ratio) is associated with age-related increases in BP and a rise in prevalence of hypertension.

Vascular Effects of Potassium Depletion:

Potassium restriction causes a deficit in cellular potassium. This triggers cells to gain sodium in order to maintain their tonicity and volume.

Population studies have shown an inverse relation between potassium intake and BP, the prevalence of hypertension, and the risk of stroke.

Cardiovascular Effects of Potassium Supplementation:

A meta-analysis concluded that potassium supplementation (> than 2.3 grams) lowered BP by an average of 4.4/2.5 in hypertensive subjects and by 1.8/1.0 in normotensive subjects. The effect was greater at higher levels of sodium excretion.

Potassium supplementation can reduce the need for anti-hypertension medication. One study reported that with an increased dietary potassium intake in hypertensive subjects, 81% of the subjects needed less than half of their baseline medication and 38% required no antihypertensive medication as compared with 29% and 9% respectively in the control group.

The DASH trial of a diet rich in fruits and vegetables, reduced BP by 7.2/2.8 at a constant level of sodium intake.

Forms of potassium that do not contain chloride, such as found naturally in fruits and vegetables, offer lager cellular entry in exchange for sodium, and greater anti-hypertensive effects.

Sodium sensitivity, defined as an increase in BP in response to a sodium intake higher than baseline, occurs in many normotensive as well as hypertensive subjects. In normotensive subjects, it appears to be a precursor of hypertension. Dietary potassium exerts a powerful dose-dependent inhibitory effect on sodium sensitivity.

Lack of Adaptation of the Kidneys to the Modern Diet:

Human kidneys are poised to conserve sodium and excrete potassium. Prehistoric humans (with low sodium intake) were well served by this mechanism. The kidneys account for 90% or more of the body's potassium loss. This mechanism is not fit for the sodium-rich and potassium-poor modern diet. The end result of the failure of the kidneys to adapt to this diet is an excess of sodium and a deficit of potassium in hypertensive patients. A low-potassium diet leads to inadequate conservation of potassium by the kidneys; a high sodium intake increases excretion of potassium.

Exchangeable sodium (measured by the isotope-dilution technique) is increased in hypertensive subjects, and correlates with arterial pressure. Exchangeable potassium correlates negatively with arterial pressure in primary hypertension.

Sodium Retention, Potassium Depletion, and Hypertension:

A. Effects on the arterial wall:

Sodium retention increases sodium concentrations and decreases potassium concentrations in the intra-cellular fluid. This results in a rise in intracellular calcium which triggers contraction of vascular smooth muscle.

Endothelium dependent vasodilation is defective in primary hypertension. Sodium retention decreases synthesis of nitric oxide, thereby decreasing arteriolar vasodilation. Increases in serum potassium, even within the physiological range, cause endothelium-dependent vasodilation.

The long-term antihypertensive effect of low-dose thiazide diuretics reflects not hypovolemia, but mainly decreased systemic vascular resistance caused by changes in the ionic composition of the vascular wall.

Natriuresis triggers cellular sodium loss, and the redistribution of potassium into cells. This contributes to thiazide-induced vasodilation.

B. Effects on the brain:

Changes in concentrations of sodium and potassium in the cerebrospinal fluid have substantial effects on BP. Increasing the concentration of sodium in the cerebrospinal fluid by intra-ventricular administration of hypertonic saline raises BP; increasing the concentration of potassium by administration of potassium chloride has the opposite effect. Increases in dietary sodium chloride increase the concentrations of sodium in the cerebrospinal fluid.

C. Effects on metabolism:

Potassium depletion inhibits insulin secretion and is associated with glucose intolerance. Potassium infusion and hyperkalemia increase the secretion of insulin. Insulin triggers endothelium-dependent vasodilation in skeletal muscle. This response is impaired in primary hypertension.

Thiazide-induced hypokalemia worsens glucose intolerance in type 2 diabetes. Correction of hypokalemia ameliorates the glucose intolerance. Angiotensin-converting enzyme inhibitors and angiotensin II blockers promote potassium retention and are associated with lower risk of onset of type 2 diabetes. Treatment of thiazide-induced hypokalemia with potassium augments the anti-hypertensive effect of the diuretic.

Implications for Prevention and Treatment:

A modified diet that approaches the high potassium:sodium ratio of the diets of our human ancestors is a critical strategy for the primary prevention and treatment of hypertension.

Weight loss, with diets rich in fruits and vegetables, has been attributed both to the low caloric density, and to the high potassium content of these diets, which tend to increase the metabolic rate.

The Institute of Medicine recommends a daily intake of ~ 3.8 grams of NaCl for adults younger than age 50; ~3.2 grams for those age 51 to 71; ~ 2.9 grams in those older than 71. The Institute also advises adults to consume ~ 4.7 grams of potassium daily This is about twice the current US average Adoption of these recommendations would increase the dietary potassium:sodium ratio by a factor of 10, from approximately 2:10 to 20:10. This is much closer to or ancestral standard.

The National High Blood Pressure Education Program has identified both a reduction in dietary sodium and potassium supplementation as proven approaches for preventing and treating hypertension.

Following these recommendations would require a comprehensive, culture-sensitive campaign targeting both the general public and health care professionals.

Modern food processing drastically changes the cationic content of natural foods, increasing sodium, and decreasing potassium. Only about 12% of dietary NaCl originates naturally in foods. About 80% results from food processing. Little, as a percentage, is added during cooking or at the table.

NEJM May 10, 2007; 359: 1966-78 Review Article, first author Horacio J Adrogue, Baylor College of Medicine, Houston TX

1 The article presents Na and K as mmol. I have converted their figures into grams of sodium, grams of NaCl ("salt"), and grams of potassium to enhance understanding. Although some sodium is contained in natural foods, the greatest dietary quantity by far comes from prepared foods. The greatest dietary potassium is contained in natural foods, especially fruits and vegetables.

1 mmol Na = 23 mg

1 mmol Cl = 35 mg

1 mmol NaCl = 58 mg

1 mmol K = 39 mg.

A Low-Glycemic Load Diet Promotes More Weight Loss In Patients With A High Insulin-Response To Glucose.

5-2 EFFECTS OF LOW-GLYCEMIC LOAD VS LOW-FAT DIET IN OBESE YOUNG ADULTS

Three popular weight-loss diets—low fat, low carbohydrate, and low-glycemic load—have received much attention. Clinical trials have produced inconsistent results, perhaps because of methodological problems or perhaps because of inherent physiological differences between study participants.

Individual differences in insulin secretion in response to dietary composition may be a mechanism which regulates weight.

The glycemic load is the mathematical product of the glycemic index of individual foods and the total amount of carbohydrate in the foods consumed. A high glycemic load meal results in higher postprandial insulin concentrations than a low glycemic load meal, even if the caloric intake is the same. High postprandial insulin concentrations may lead to a decreased availability of metabolic fuels several hours after a meal, causing hunger and overeating. (Ie, postprandial hypoglycemia.)

Some individuals have a higher insulin response to glucose ingestion. They may be more likely to develop postprandial hypoglycemia.

This study determined if insulin secretion affects body fat loss among obese individuals consuming self-prepared diets. Low-glycemic load/higher-fat diets were compared with high glycemic-load/lower-fat diets.

Conclusion: Low-glycemic load diet may be especially important to achieve weight loss among individuals with a high insulin response.

STUDY

1. Randomized trial enrolled 73 obese young adults (mostly female; age range 18-35; mean = 27) for 18 months. All had a BMI of 30 and above. None had diabetes or other major illnesses.

2. During the first 6 months the investigators conducted an intensive intervention period of nutrition education and dietary counseling. This was followed by a 12 month follow-up period with continued counseling.
3. Prior to randomization, a 75-g glucose tolerance test determined serum insulin levels at 30 minutes. The median serum insulin concentration at this time was 58 micro-IU/mL.
4. Randomized to:
    1) Low-glycemic load diet: 40% of energy from carbohydrate (emphasizing low glycemic index foods); 35% from fat; and 25% from protein.
    2) Low-fat diet: 20% of energy from fat; 55% from carbohydrate; and 25% from protein. This diet was not designed to maximize glycemic load, but to prescribe a diet consistent with low-fat guidelines.
3. Aimed to keep treatment intensity, treatment fidelity, nutrition education, dietary counseling, and physical activity prescription the same between diet groups.
4. Diets were prescribed using an ad-libitum approach. Subjects did not receive any quantitative information regarding macronutrient targets. They were told to "eat when you are hungry, before you are famished. Stop eating when you are satisfied, before you become stuffed."
5. The investigators presumed that these investigational diets would decrease hunger, increase satiation, and therefore promote a negative energy balance.
6 Main outcome measures = body weight, body fat percentage, and risk factors for cardiovascular disease.

RESULTS

1. There was a distinct difference in weight loss at 18 months depending on the baseline serum insulin concentration.
    1) Subjects with baseline insulin concentrations greater than 58 micro-IU/mL:
        Individuals on the low glycemic load diet lost 5.8 kg
        Individuals on the low fat diet lost 1.2 kg
    2) Subjects with baseline insulin concentrations below 58 micro-IU/mL.
        Individuals on a low glycemic load diet lost about 2 kg
        Individuals on a low fat diet also lost about 2 kg.
        (Ie, insulin concentration was an effect moderator for weight loss.)
2. HDL-cholesterol and triglycerides improved on the low-glycemic load diet; LDL-cholesterol improved more on the low-fat diet.

DISCUSSION

1. For individuals with a low insulin concentration at 30 minutes after a glucose load, a low glycemic-load diet and a low fat diet produced comparable weight loss.
2. For those with high post prandial insulin concentrations, a low-glycemic load diet produced greater weight loss than the low fat diet. "Reducing glycemic load may be especially important to achieve weight loss among individuals with high insulin secretion."
3. "Thus, phenotypic differences among individuals may explain some of the variability in individual outcomes

within dietary weight-loss trials." Variability in dietary weight loss may be partially attributable to differences in hormonal (insulin) response.

4. The investigators speculate that a low-glycemic load diet in which saturated fat is kept low, and mono- and poly-unsaturated fat are higher, would result in a more favorable effect on lipids..

CONCLUSION

For obese individuals with high insulin concentrations after a glucose load, a low-glycemic diet may promote more weight loss than a low-fat diet.

Regardless of insulin secretion, a low-glycemic load had beneficial effects on HDL-cholesterol and triglyceride levels, but not on LDL-cholesterol.

NEJM May 18, 2007; 297: 2092-2102 Original investigation, first author Cara B Ebbeling, Children's Hospital Boston, Boston Mass.

Study supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda MD.

This was a difficult and involved study, much more complicated than I have indicated. I congratulate the subjects and the investigators on their dedication.

One interesting aspect of the study—the diets were ad lib. No calorie counting or limitation on the quantity of food intake was involved. Intake was determined by the subjects' feeling of satiety.

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5-3 OSTEOPENIA

Bone mineral density (**BMD**; expressed as grams per square centimeter) is a better predictor of fracture than BP is of stroke. The relative risk of hip fracture is 2.6 for each 1 standard deviation (**SD**) decrease in BMD at the hip. The relative risk of fracture is continuous, with no absolute cutoff value to define a pathological state.

The WHO has defined diagnostic categories of BMD:

Normal	BMD within 1 SD of the reference mean for young adults
Osteo-*penia*	BMD more than 1.0 SD but less than 2.5 SD below the mean
Osteo-*porosis*	BMD 2.5 SD or more below the mean
Severe osteoporosis	BMD 2.5 SD or more below the mean with one or more fragility (low trauma) fractures

The SDs are termed "T-scores".

An estimated 33 million Americans (80% women) have osteopenia. Osteopenia is analogous to pre-hypertension, impaired fasting glucose, and borderline high cholesterol in defining an intermediate-risk group with somewhat uncertain boundaries.

Although the risk of fracture is greater among persons with osteoporosis than among those with osteopenia, the much larger numbers of persons with osteopenia than with osteoporosis (39% vs 6% in primary care practice) means that the numbers of fractures observed will be greater among person with osteopenia.

A clinical dilemma posed by osteopenia arises when a BMD in the osteopenic range is identified in patients without an obvious indication for drug treatment. (such as a fragility fracture). Additional factors may help identify patients with osteopenia who are at increased risk for fracture as compared with others with similar values for BMD, and may influence clinicians to treat osteopenia earlier:

Age (over 65)

Female sex

Personal history of fragility fracture as an adult over age 50 (The single best predictor is a previous fracture)

History of fragility fracture in a first degree relative

Low body weight (BMI 20)

Current smoking

Excessive alcohol ingestion (> 2 drinks per day)

A propensity of elders to fall, poor vision, dementia, low calcium intake, and physical frailty are other indications.

(*Administration of corticosteroids, and recently selective serotonin re-uptake inhibitors [SSRIs], which are used commonly in depressed older patients, have been reported to increase risk of bone loss.)*

Treatment:

In persons at increased risk of fracture, clinicians must decide whether to recommend lifestyle interventions, or drug therapy in addition to lifestyle interventions:

Lifestyle:*

Calcium intake 1200 to 1500 mg daily

Vitamin D 400 to 800 IU daily

Weight bearing exercise

Stop smoking

Limit alcohol consumption

(I believe too late to do much good. Compliance will likely be low.)*

Pharmacological:

"The FDA has approved a number of drugs for the *prevention* of postmenopausal osteoporosis." These include bisphosphonates, selective estrogen-receptor modulators, and estrogens. All of these agents attenuate ongoing bone loss. Data are limited regarding their efficacy in reducing the risk of fractures in women with osteopenia. Trials of bisphosphonates have reported conflicting results in women with T-scores above -2.5.

Decisions regarding drug therapy must take into account the long period of treatment (at least 5 to 10 years), and sometimes indefinitely. This may not represent a cost-effective use of health-care resources.

Guidelines:

The American Osteoporosis Foundation and others recommend treatment for patients with osteoporosis (as defined above), and for all with a fragility fracture. They recommend *against* drug treatment for patients with T-scores higher than -1.0.

Recommendations for osteopenia are inconsistent.

Some groups suggest at least the consideration of pharmacological therapy for women with T-scores that are less than -1.5 who have additional risk factors. Some recommend that drug intervention be deferred until the T-score is -2.0 to -2.5, even if additional risk factors are present.

Conclusions and recommendations:

The lifetime risk of osteoporotic fracture is 40% in women and 13% in men. Because osteopenia is much more common than osteoporosis, the majority of fragility fractures occur in patients with osteopenia. Measurements of bone mineral density alone cannot effectively discriminate between patients with osteopenia who will have fractures, and those who will not.

"Clinical risk factors should be considered in combination with measurement of bone mineral density to estimate fracture risk and guide investigation." The patient's own evaluation of risks and benefits should influence the choice between lifestyle treatment alone or lifestyle + drug therapy.

"Unless the patient strongly prefers to take anti-resorptive medication, or has a T-score near the osteoporotic range with several risk factors for fracture, encouragement of lifestyle modifications with reassessment in 2 to 3 years is a reasonable strategy, and is our recommendation for the majority of patients with osteopenia."

NEJM May 31, 2007; 356: "Clinical Practice" a review and opinion article, first author Sundeep Khosla, Mayo Clinic College of Medicine, Rochester Minn.

Sponsored by grants from the National Institutes of Health,

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5-4 IRRITABLE BOWEL SYNDROME: Clinical Update

- IBS is one of the most common reasons for consultation. Because the disorder is poorly understood many doctors find it difficult to treat. Successful management is rewarding because it can substantially improve quality of life.
- Under the Rome III diagnostic criteria, IBS affects about 5% of the population:

  Recurrent abdominal pain. or discomfort (uncomfortable sensation not described as pain; eg, bloating) associated with two or three of:

  Improvement of the symptom with defecation

  Onset associated with change in frequency of stool (constipation or diarrhea)

  Onset associated with change in form (appearance; consistency) of stool.
- Stool consistency may be predominantly hard (constipated); loose (diarrhea); or mixed (alternating between the two).

- Patients are typically female age 20 to 40. Most symptoms occur intermittently with flares lasting 2 to 4 days. Symptoms usually persist for years. A symptom-based diagnosis can be safely made in cases meeting the criteria in the absence of alarm symptoms.
- Hypersensitivity to visceral sensation is common and appears to be partly caused by failed anti-nocioceptive pathways.
- Many patients correctly believe that their symptoms are aggravated by meals. About 1/3 have associated functional dyspepsia.
- Patients often have several non-gastrointestinal somatic symptoms (lethargy, headache, backache, urinary symptoms, and dyspareunia). They may have a history of frequent consultations and medically unexplained symptoms. IBS is associated with psychological distress. About half of patients who seek medical care for IBS are depressed or anxious.
- The physical examination is usually normal. Poorly localized tenderness may be present.
- Alarm symptoms should alert the physician to exclude more serious diseases:
  - Age over 50 at onset
  - Male
  - Short history of symptoms
  - Nocturnal symptoms
  - Family history of colon cancer
  - Rectal bleeding
  - Recent antibiotic use
- If diarrhea is present, bowel inflammation and malabsorption should be investigated, including serology for celiac disease. (Celiac disease is present in 3-5% of IBS patients in the UK.)
- Most IBS patients require reassurance, explanation, and lifestyle advice. Most patients believe that they have serious disease. Reassurance is important. Psychological treatment may improve coping, but often without change in bowel habits.
- Dietary modification may be tried. Wheat and dairy products have been described as aggravating symptoms. Lactose intolerance is worth considering in patients with diarrhea.
- Drug therapy is the preferred intervention by both doctors and patients. There is a large placebo effect.
  - Antispasmodics may improve pain (first choice when pain predominates)
  - Soluble fiber for constipation
  - Loperamide (Generic; *Immodium*, McNeil Consumer) for diarrhea (may reduce bowel frequency, but does not help pain)
  - Tricyclic antidepressants (of uncertain value; data is old). Amitriptyline (Generic; *Elavil*) especially at low doses, for patients with diarrhea has been reported as beneficial.
  - Selective serotonin-reuptake inhibitors (eg, fluoxetine; *Prozac*, Lilly). Experience is limited.
    - One small trial reported global improvement, with no significant improvement in bowel symptoms.

Lancet May12, 3007; 369: 1586-88 Review article by Roger Spiller, University Hospital, Nottingham, UK

The author states that a symptom-based diagnosis can be safely made in cases meeting the Rome criteria in the absence of alarm features, and if the physical examination is normal. Further investigations are unlikely to detect any abnormality.

I would keep my mind open for other possible causes of the symptoms, and follow up carefully to determine that the patient remains stable. See a following article on celiac disease.

The large number of different drugs used therapeutically indicates that treatment is empirical and no drug provides satisfactory relief in all patients.

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Should Not Be Greater Than 75 or 81 Mg/Day.

5-5 ASPIRIN DOSE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

"No drug is used by greater number of people world wide than aspirin." An estimated 50 million people in the US take aspirin regularly for long-term prevention of cardiovascular disease (**CVD**). The great majority of individuals with known CVD also take aspirin.

Patients in the US are typically prescribed either 81 mg or 325 mg daily. Although generally well tolerated, aspirin carries a significant risk of adverse effects, many of which are dose-related.

Maximizing benefits and minimizing risks by providing optimal dosing is important. Randomized trials to confirm benefits of aspirin in treatment and prevention of atherosclerotic disease have used doses ranging from 50 to 1300 mg/day. The FDA recommends these doses for treatment of the clinical manifestations of atherosclerotic disease.

This study reviews the mechanism of action of aspirin, and the relationships among aspirin dosage, efficacy, and safety for patients with CVD.

Conclusion: For cardiovascular disease prevention, dosages should not be greater than 75 or 81 mg/day.

STUDY

1. This systematic review analyzed 11 studies of aspirin therapy for CVD.

RESULTS

1.Therapy requiring an immediate effect (eg, acute myocardial infarction, TIA, stroke):

Aspirin taken orally is rapidly absorbed. Peak plasma levels are achieved rapidly (30 minutes).

Aspirin rapidly acetylates and inactivates platelet COX-1. This leads to rapid inhibition of thromboxane production, accounting for its benefits and adverse effects.

A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to achieve maximal antiplatelet activity. Absorption and onset of antiplatelet activity are shortened by chewing the tablet or drinking a solution (eg, *Alka-Seltzer*). Maximum inhibition of thromboxane production is achieved in 20 to 30 minutes compared with swallowing a whole aspirin tablet (60 minutes). To rapidly achieve maximal antiplatelet activity of aspirin at least 163 mg should be chewed or dissolved and then swallowed. [1]

2. Long-term therapy:

Aspirin irreversibly inactivates platelet COX-1. De-novo synthesis of new COX-1 by platelets is minimal. The long-term effects of aspirin on platelets are cumulative.

Once complete inactivation of platelet COX-1 is achieved, minimal doses of aspirin are required to ensure adequate acetylation of COX-1 and inactivation of thromboxane production. New platelets containing the normal amounts of COX-1 are formed at a rate of 10% daily. As little as 30 mg of aspirin daily is required to completely inhibit thromboxane production in healthy individuals. In patients with chronic stable angina, thromboxane synthesis is chronically elevated and 50 mg of aspirin daily may be needed.

Enteric coated aspirin is also used routinely in the setting of long-term use. Questions have been raised regarding the effect of the coating on bioavailability and biological action of aspirin. Evidence is conflicting. Some reports suggest it has a lower level of inhibition of thromboxane compared with uncoated aspirin.[2]

3. Clinical efficacy:

The clinical benefit of aspirin in short-term treatment and long-term prevention of manifestations of atherosclerotic disease (stroke, transient ischemic attacks, myocardial infarction, percutaneous coronary interventions, carotid endarterectomy, and peripheral interventions) have been conclusively demonstrated.

A number of trials and meta-analyses have evaluated the optimal aspirin dose in various clinical settings. “The one nearly constant finding among all of these studies has been the lack of a relationship between increasing aspirin dosage and improved efficacy. In fact, the trend in benefit has almost uniformly favored lower dosages.”

The 11 trials reviewed by this study included nearly 10 000 patients with atherosclerotic disease receiving doses of 30 to 1300 mg per day). A significant benefit of higher doses was not demonstrated in any trial. In most trials, the lowest event rates were realized among patients randomized to the low-dose groups.

There is evidence that a sex difference exists in clinical response to aspirin. In a meta-analysis of trials of primary prevention, aspirin was associated with a significant reduction in MI in men, but had no effect in preventing stroke. The opposite occurred in women.

4. Adverse effects:

The major risk of aspirin (as with other NSAIDs) is bleeding—the majority from the g.i. tract. Although this increase is more commonly attributed to non-aspirin NSAIDs, a recent evaluation of patients hospitalized for ulcer bleeding found that aspirin was responsible for as much ulcer bleeding as all other NSAIDs combined. Low-dose aspirin was one of the most common causal agents.

Aspirin inhibits COX-1 in the gastric mucosa (as well as in platelets) and decreases the production of prostaglandins which protect the gastric mucosa. The influence of aspirin on gastric prostaglandins is dose-dependent. Almost 50% inhibition occurs at 30 mg / day—maximal inhibition at 1300 mg / day. “All conventional doses of aspirin are associated with increased bleeding risk.” But, a relationship between higher aspirin dose and increased risk of bleeding has been demonstrated in clinical trials. A UK trial found almost double the risk among patients randomized to 1200 mg/day compared with 300 mg/day. A Dutch trial found a

trend toward less bleeding in the group receiving 30 mg/day compared with 283 mg/day. However, not all pooled study analyses have come to the same conclusion.

Considering that 50 million Americans are taking daily aspirin, if there is a difference in risk of major g.i. bleeding between 30 mg and 325 mg, then the larger dose would lead to an excess of 900 000 major bleeding events per year.

Enteric-coated or buffered aspirin preparations do not appear to reduce the risk of major bleeding in the upper g.i. tract"[2]

CONCLUSION

Although, in general aspirin is safe, when it is used in large populations, even a low overall incidence of adverse effects can have a substantial impact.

An association between increases in aspirin dose and adverse effects has been confirmed. No such dose relationship has been identified for efficacy.

This suggests that following the rapid acute inhibition of platelet COX-1 with 325 mg (as in treatment of acute MI[1]), every effort should be made to minimize the long-term dose.

Currently available clinical data do not support the routine, long term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher doses are associated with increased risks of gastrointestinal bleeding.

JAMA May 9, 2007; 297: 2018-24 "Clinical Review" first author Charles L Campbell, University of Kentucky, Lexington.

1 I believe this is an important clinical point. Reducing the ischemia of an acute MI by even a few minutes may improve prognosis. I still wonder at the remarkably beneficial effects of aspirin in patients with acute myocardial infarction. Think—of all the years that went by when a simple home remedy (a 325 mg tablet) contained in almost every bathroom cabinet was immediately available, and its value was not appreciated.

2 I continue to consider that aspirin may have a locally irritating effect on the stomach mucosa. Would not this, in addition to its systemic effects on platelets, add to the risk of bleeding? Since cost difference is nil, I would take coated aspirin long-term. Can anybody out there help me on this point? Does anyone have more definitive data on safety of enteric coated aspirin?

For my edification, I reviewed and simplified the physiological activity of platelets—I hope accurately:

Platelets contain:

1) Arachidonic acid—an unsaturated fatty acid; a biological precursor of thromboxane

2) Cyclo-oxygenase-1 (COX-1), an enzyme which converts arachidonic acid into thromboxane.

Thromboxane is a 20 carbon atom prostanoic acid (a prostaglandin) produced from arachidonic acid.

by the action of platelet COX-1

When platelets are activated by contact with sub-endothelial connective tissue they are activated immediately, releasing the newly formed thromboxane which causes vasoconstriction and platelet aggregation (primary hemostasis as contrasted with secondary hemostasis—the clotting cascade).

A single dose of aspirin acetylates platelet COX-1 and prevents thromboxane production. Platelets are not nucleated. Their contents cannot be replenished. Their life span is about 10 days. Completely replenishing platelet COX-1 takes 10 days.

A separate effect of the COX-1 is related to bleeding from the stomach. COX-1 in the stomach normally leads to production of a prostaglandin which protects the stomach mucosa. Aspirin (and other NSAIDs) inhibit action of stomach COX-1. Production of prostaglandins which protect the stomach endothelium is impaired. A protective effect is lost. Bleeding tendency is increased. Upper g.i. bleeding must also be related to impaired platelet function.

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Effective Prophylaxis. Not Effective Treatment

5-6 QUADRIVALENT VACCINE AGAINST HUMAN PAPILLOMAVIRUS TO PREVENT HIGH-GRADE CERVICAL LESIONS

Cervical cancer is the second most common cancer in women, and the leading cause of cancer-related death in many developing countries. Human papillomaviruses (**HPVs**) cause virtually all cervical cancers. Types 16 (HPV-16) and type 18 (HPV-18) cause about 70%.

When phase 3 trials of a HPV vaccine were in the planning stage, the FDA recommended that the trials be powered to demonstrate efficacy in preventing high-grade cervical intraepithelial neoplasia (CIN) grades 2 and 3.

This article reports the results of a phase 3 trial of quadrivalent vaccine against HPVs 6, 11, 16, and 18 designed to assess the prevention of CIN grade 2 and 3, cervical adenocarcinoma in situ, and cervical cancer caused by HPVs 16 and 18. (HPVs 6 and 11 are rarely detected in high-grade CIN. They do cause the majority of anogenital warts.)

Conclusion: The vaccine was very effective in females who had not previously been infected with HPVs 16 and 18.

STUDY

1. Multicenter, multicountry randomized, double-blind trial assigned over 12 000 women between ages 15 and 26 (mean = 20) to: 1) three doses of the vaccine, or 2) placebo injections. Injections were given at day 1, month 2, and month 6. The vaccine (*Gardasil*; Merck) contained an aluminum hydroxide adjuvant.
2. On the first visit after randomization, a gynecological examination was performed which included a cervical Pap smear, and swabs for HPV-DNA testing.
3. No subjects were pregnant, none had abnormal results on a Pap smear. At baseline, about 10% in both groups were positive for HPV-16 or 18 by PCR, and 4% positive by serology. These subjects were included in the original randomization.
3. The primary analysis included only women (5300 vaccine, and 5200 placebo) who had no virological evidence of HPV 16 and 18 infections through 1 month after the third dose (month 7).
4. Primary composite endpoint = CIN 2 and CIN-3, adenocarcinoma in situ, or cervical cancer related to HPVs 16 and 18.
5. Follow-up for an average of 3 years after receiving the first dose of vaccine.

RESULTS

1. Vaccine efficacy for prevention of the primary composite endpoint:
   A. Efficacy was almost 100% in the susceptible population (n = 10 565). Only one vaccinated individual who was without HPV infection at baseline (determined by PCR or serology) developed cervical intraepithelial neoplasia (CIN-3). This single subject was positive for HPV-52 at baseline.
   B. Vaccination was not effective in those who were positive for HPV-16 or 18 at baseline. (n = 782) In this group there were 98 cases of CIN-2 or 3, and 5 cases of adenocarcinoma in situ—most due to HPV-16.
   C. More of these cases occurred in the placebo group.
   D. None of the subjects developed invasive cervical cancer.

DISCUSSION

1. When administered to subjects who had not been previously exposed to either HPV-16 or HPV-18, the vaccine was highly effective in preventing HPV-16, and HPV-18 related cervical intraepithelial neoplasia grade 2 and 3, and adenocarcinoma in situ.
2. Efficacy was lower for the population of all women who were randomized. This included women who had HPV-16 or HPV-18 infections before the first injection.
3. It is ethically unacceptable to use invasive cancer as the endpoint in efficacy trials. Cervical intraepithelial neoplasia and adenocarcinoma in situ are clinically important outcomes. They are likely to persist and may become invasive.
4. Previous phase 2 trials found no evidence of waning immunity up to 4 to 5 years after vaccination.
5. There was no clear evidence that vaccination altered the course of HPV-16 or HPV-18 infections which were present before administration of the vaccine. (Ie, the vaccine is prophylactic, not therapeutic.)

CONCLUSION

In young women who had *not* previously been infected with HPV-16 or HPV-18, vaccination significantly lowered the occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18.

Widespread immunization of female children and adolescents may result in substantial decrease in HPV-16 or HPV-18 related cervical disease, including cervical cancer.

NEJM May 10, 2007; 356: original investigation by the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE-II) Study Group, Request for reprints to Laura A Koutsky, University of Washington, Seattle. Study supported by Merck.

HPV infections are very common sexually-transmitted diseases.

There was no protection against a number of other HPVs which may cause cervical lesions and cancer.

There was no protection against cervical lesions caused by HPV-16 and HPV-18 which were present at the time of vaccination. Thus, it has been advised that girls be vaccinated at ages 11 and 12, before sexual activity begins.

(What about males?)

Vaccination does not eliminate the need for continuing screening for cervical cancer.

See also in this issue of NEJM:

Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases. (pp 1928-43)

The vaccine reduced incidence of anogenital lesions due to the virus.

Case-control Study of Human Papillomavirus and Oropharyngeal Cancer. (pp 1944-56)

Evidence that HPV is associated with oropharyngeal cancer with or without tobacco and alcohol use.

See also Lancet May 19, 2007; 369: 1693-1702 "Efficacy of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) against high-grade vulvar and vaginal lesions" The vaccine was effective in preventing these lesions.

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"Most Cases Are Unrecognized"

5-7 COELIAC DISEASE IN PRIMARY CARE

Celiac disease (**CD**) is characterized by a life-long intolerance to certain proteins (known collectively as gluten) contained in wheat, rye, and barley. It is an unusual combination of food intolerance and auto-immunity. The resultant chronic inflammation of the proximal small intestine results in atrophy of villi, and abnormal intestinal permeability with impaired absorption of nutrients and increased secretion of solids.

In classical CD, patients have intestinal malabsorption and gastrointestinal symptoms.

Atypical CD (the most common form) has few or no gastrointestinal problems. But, there are other problems: iron deficiency anemia, osteoporosis, short stature, infertility, and unfavorable outcome of pregnancy.

CD is more common in people who have first degree relatives with the condition, and in patients with iron deficiency anemia, low bone mineral density and auto-immune disorders (type 1 diabetes, auto-immune thyroid and liver disease). It is also associated with excess death rates and increased risk of Hodgkin's lymphoma and other cancers.

CD affects about 1% of the general population. Most cases are unrecognized. Diagnosis is often delayed. "This is surprising, given how common the disease is, and how seriously its effects can be." It may be because most patients with CD do not have typical symptoms of malabsorption. Even if these symptoms are present, their non-specific nature may not trigger diagnostic suspicion of the disease.

The gold standard for the diagnosis of CD is a positive duodenal biopsy. Quadratic biopsies from the duodenum are needed because the histology of the disease can be patchy. Even then, the preparation and interpretation of histological material may create diagnostic uncertainty. Follow-up and re-investigation may be needed to confirm the diagnosis.

In primary care, the American Gastroenterology Association recommends the use of antibody to transglutaminase (an enzyme present in many tissues) as the single diagnostic serological test.

A gluten-free diet corrects anemia, and restores normal nutritional and biochemical status. It substantially improves quality of life, particularly if troublesome gastrointestinal symptoms have been present.

This issue of BMJ[1] reports a validated clinical prediction rule to determine all cases of celiac disease in people referred for gastroscopy:

The study followed 2000 patients referred for gastroscopy. All received 1) test for antibody to transglutaminase*, and 2) duodenal biopsy.

A. They classified patients as being at

1) “High risk” for CD. (N = 739 with diarrhea, weight loss, and/or anemia), or

2) “Low risk” (N = 1261) All other patients with indications for gastroscopy: abdominal pain; reflux; dyspepsia; nausea and vomiting, and chest pain. (Ie, not suggestive of CD.)

(* a commercially available enzyme-linked immunosorbent assay to measure IgA antibodies to tissue transglutaminase. Transglutaminase is an enzyme which cross-links glutamine in proteins to lysine in proteins. It is ubiquitous in tissues. In celiac disease, IgA auto-antibodies develop to transglutaminase. A relatively simple serological test can determine the concentrations of the antibodies in blood.)

B. Results;

1) High risk patients (n = 739)

Antibody to transglutaminase positive (n = 154; CD diagnosed by biopsy in 64 [40%])

Antibody to transglutaminase negative (n = 585 CD diagnosed by biopsy in 7 [1.2%])

2) Low risk patients (n = 1161)

Antibody to transglutaminase positive (n = 91; CD diagnosed by biopsy in 6 [7%])

Antibody to transglutaminase negative (n = 1170; CD diagnosed by biopsy in none [0%])

C. The investigators concluded:

1) If the patient has high risk symptoms and a positive test for antibody to transglutaminase, duodenal biopsy should be done. (About 40% of these patients actually had CD.)

2) If the patient has high risk symptoms and a negative antibody test, biopsy should be done nevertheless. (CD is less common. Only 1.2% had CD. But these patients should not be missed.)

3) If the patient has low risk symptoms, and the antibody test is positive CD may be present in a few (6%), and a biopsy should be done.

4) If the patient has low risk and the antibody test is negative, a biopsy is not needed. CD was not present in any patients in this group (0 of 1170).

D. Their prediction rule:

Antibody to transglutaminase may be used as a primary screen in suspected cases of CD.

All patients with a positive antibody to transglutaminase should be biopsied.

All patients with a clinically “high risk” of CD should be biopsied regardless of results on the antibody test.

Patients at “low risk” of CD, and a negative antibody test do not require biopsy.

What are the important messages for primary care?

1) Patients with unexplained diarrhea, anemia, weight loss, infertility, recurrent miscarriages and low birth weight babies should be investigated for CD.

2) Risk of CD is higher in patients with a first degree relative with the condition or with other auto-immune disorders. (CD sometimes shares HLA markers with other auto-immune disorders.)

3) All patients with positive antibodies to transglutaminase should have a duodenal biopsy.
4) While a life-long gluten free diet can reverse the effects of gluten enteropathy, the diagnosis must be confirmed by a biopsy before advising this difficult life-style intervention

BMJ April 7, 2007; 334: 704-05 Editorial by Roger Jones, KCL School of Medicine, London, UK

The article used "coeliac: disease (British spelling)

1 "Pre-endoscopic serological testing for coelic disease" BMJ April 7, 2007; 334: 729-32 First author Andrew D Hopper, Royal Hallamshire Hospital, Sheffield, UK

See also "Reaching a milestone in diagnosing ceoliac disease" BMJ April 7, 2007; 334: 732-33 "Commentary, first author Mark L Graber, VA Medical Center, Northport NY, USA.

The rule is simple. It identified every patient with CD in a cohort of 2000 patients, all of whom underwent duodenal biopsy (as the gold standard) as the final diagnostic step. "This is a welcome advance. As the authors emphasize, coeliac disease may affect up to one in 100 people, only one is ever diagnosed, and an appreciable delay of many years often occurs."

The population studied was a referral cohort. In other settings the base rate of CD will probably be lower.

The study strongly validates an approach that allows us to estimate with some confidence probabilities of success or failure at each step of the process. The results support the current practice of forgoing endoscopic biopsy in low risk patients with negative serology. None of 1170 patients meeting these criteria in the study had CD on biopsy.

However, even if the antibody test was positive in "high risk" patients, the minority actually had CD.

Positive results of serology not sufficient to diagnose. Biopsy is still essential, especially if the patient is to be placed on a life-long gluten-free diet.

What about patients with "high risk" symptoms who have a negative antibody test? The study recommends biopsy in these patients as well. However, this approach identified only 7 additional cases of CD out of 585 biopsied.

Problems remain—variability of the definition of "high risk" may occur in primary care. The results of testing for antibody to transglutaminase may vary in different laboratories. The interpretations of biopsies and the quality of biopsy samples may not be uniform.

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Prognosis Is Better With Ruptured Disk Than With Spinal Stenosis.

5-8 BACK SURGERY—WHO NEEDS IT?

Surgery is not the final common pathway for everyone with persistent back pain. It offers specific therapy for specific anatomical derangements associated with specific derangements.

A generation ago, "back surgery" usually meant removing the offending portion of a herniated disk. Times have changed. Indications and surgical techniques have expanded. Indeed, clinical science has struggled to keep pace with innovation, creating uncertainties about the efficacy and safety of new surgical techniques.

Despite assertions that surgery is only a last resort, and is used more selectively than in the past, spine surgery has steadily increased over the past decades.

Are the benefits of surgery worth the risks?

Two studies in this issue of NEJM [1,2] help define the type of patients who may benefit from surgery.

The first study randomized patients with severe sciatica due to herniated disks. None had resolution of pain within 6 to 12 weeks prior to randomization. Patients were randomized to 1) early diskectomy, or 2) non-surgical therapy, or delayed surgery.

Reserving surgery for patients whose pain did not sufficiently improve for 6 to 12 weeks of non-surgical treatment is important because sciatica improves spontaneously within 3 months in 75% of patients.

Even among patients with persistent sciatica, recovery was likely whether or not surgery was performed. Most herniated disks shrink over time. But surgery accelerates the pace of recovery, and for some patients faster recovery may be worth the risks.

After a year, however, recovery was about the same with non-surgery as with surgery (95% in both groups), although almost 40% of patients initially assigned to the non-surgical group crossed-over to surgery.

"Thus, for patients with persistent sciatica, there seems to be a reasonable choice between surgical and non-surgical treatment, which may be influenced by aversion to surgical risks, the severity of symptoms, and willingness to wait for spontaneous healing." *(Ie, patients' choice depends on full explanation, negotiation between surgeons and patients, and patients' perception of the severity of pain and degree of disability. The large percentage of patients who crossed over from non-surgery to surgery suggests that many perceived severe pain and disability.)*

The second study addressed degenerative spodylolisthesis with associated spinal stenosis. This condition causes both back and leg pain. The study was randomized, but there were so many unintended crossovers from the non-surgical group to the surgical group that the authors highlighted their analysis according to treatment received rather than intention-to-treat, essentially creating a single large cohort study. *(Again indicating that many patients perceived a high degree of pain and disability.)*

About 95% of surgical patients underwent a spinal fusion procedure. Thus, the study was essentially a trial of fusion for spodylolisthesis. Fusion surgery is more invasive than diskectomy, with higher complication rates. Patients are usually older than those undergoing surgery for ruptured disk. Surgical complication rates increase substantially after age 80.

The study reported that surgery offered a significant advantage over non-surgical therapy, although the possibility of confounding could not be eliminated and the benefits of surgery may have been overestimated or underestimated.

"The study further solidifies the basis of performing spinal fusion in patients with persistent leg pain, spodylolisthesis, and associated spinal stenosis."

Previous studies of non-surgical treatment for spinal stenosis suggested a low rate of spontaneous improvement in contrast to the more favorable results of non-surgical treatment for herniated disks.

In the two trials, both back pain and leg pain were ameliorated by surgery, but leg pain resolved more quickly and fully than back pain. Benefits were likely to be greatest for nerve-root associated symptoms.

NEJM May 31, 2007; 356: 2239-43 "Perspective" by Richard A Deyo, University of Washington, Seattle.

(Good illustrations pp 2240-41-41)

1 "Surgery versus prolonged conservative treatment for sciatica" NEJM May 31, 2007; 356: 2245-56 Original investigation, first author Wilco C Paul, Leiden University Medical Center, Leiden, the Netherlands.

The trial assigned patients who had severe sciatica, which did not resolve for 6 to 12 weeks, to early surgery or to prolonged conservative treatment, with surgery if needed. 39% of those assigned to conservative treatment crossed –over to surgery after a mean of 18 weeks.

Relief of leg pain and perceived recovery were faster in the early surgery group.

At one year, perceived recovery was 95% in both groups.

2 "Surgical versus non-surgical treatment of lumbar degenerative spodylolisthesis" NEJM May 31, 2007; 356: 2257-70 Original investigation, first author James N Weinstein, Dartmouth Medical School, Lebanon, NH.

Degenerative spodylolisthesis is the slipping forward of one lumbar vertebra on another (usually L4 on L5). The neural arch remains intact. It. rarely occurs before age 50. Spodylolisthesis is generally asymptomatic, but it can be associated with symptomatic spinal stenosis.

Degeneration of the disk between L4 and L5 allows the forward displacement of L4 on L5. It is accompanied by degenerative changes in the facet joints. The process may occur with or without spinal stenosis. The degenerative (hypertrophic) changes in the facet joints may be accompanied by thickening of the ligamentum falvum on the posterior aspect of the vertebral canal. This may result in a narrowing of the spinal canal (spinal stenosis) and compression of nerve roots. (*Illustration page 2240*)

Patients typically present with neurogenic claudication—pain in the buttocks and legs with walking or standing that resolves with sitting or lumbar flexion.

Anatomical spinal stenosis is frequently detected by imaging studies. Clinical correlation between symptoms and imaging is critical.

Management of degenerative spodylolisthesis with spinal stenosis is controversial. Surgery is widely used, but its effectiveness in comparison with non-surgical treatment has not been demonstrated in controlled trials.

The study enrolled over 600 patients (mean age 66) with at least 12 weeks of symptoms and image-confirmed degenerative spodylolisthesis.

At 2 years, treatment outcomes were determined in 511 patients. In all outcomes measured, including improvement in pain and functioning, surgery was superior to non-surgical care.

Patients' ratings surgery vs no-surgery:

Very or somewhat satisfied with symptoms 69% vs 32%

Self-rated major improvement 74% vs 24%

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Modest Exercise For Little Over An Hour A Week Had A Training Effect.

5-9 EFFECTS OF DIFFERENT DOSES OF PHYSICAL ACTIVITY ON CARDIORESPIRATORY FITNESS AMONG SEDENTARY, OVERWEIGHT OR OBESE POSTMENOPAUSAL WOMEN WITH ELEVATED BLOOD PRESSURE

Low fitness is a powerful, independent risk factor for premature mortality. Improvements in fitness are associated with reduced mortality risk. Continuing to identify and refine efficient, safe, and acceptable exercise prescriptions is of substantial public interest.

Cardiovascular disease is the primary cause of death in postmenopausal women (30% of these women report no physical activity at all). The presence of inactivity increases with age. Fitness declines at 1% to 2% per year during the postmenopausal years. Physiological changes associated with aging may decrease the body's ability to maintain or improve fitness.

The NIH consensus panel recommends at least 30 minutes of moderate-intensity physical activity on most days.

There are unanswered questions:

Will sedentary individuals obtain improvements in fitness if they perform less than 30 minutes of activity on most days?

If individuals perform more exercise than recommended, will they obtain proportionally greater improvement in fitness?

This trial examined the effect of 50%, 100%, and 150% of the NIH physical activity recommendations on cardio-respiratory fitness in sedentary overweight, or obese, postmenopausal women with elevated BP.

Conclusion: Women experienced a graded dose-response change in fitness across levels of exercise training.

STUDY

1. Randomized, dose-response exercise trial entered 464 volunteer postmenopausal women (age 45 to 75; mean = 57). None had a history of cardiovascular disease or any other serious medical condition.
2. All were sedentary (not exercising over 20 minutes on more than 3 days per week and taking less than 8000 steps/day assessed by pedometer) .
3. All were overweight or obese (mean BMI = 32); mean BP = 140/81.
4. Measured at baseline: mean energy intake = 2238 kcal / day; maximal heart rate = 151; peak absolute VO2 = 1.3 L/min.
5. Randomized to:

   1) Non-exercise group asked to maintain their usual daily activity.

   2) Exercise groups:

      4 kcal/kg/wk. (50% of recommended exercise level)

      8 kcal/kg/wk. (100% of recommended exercise level)

      12 kcal/kg/wk. (150% of the recommended exercise level)

   (The 8 and 12 kcal/kg/wk groups gradually increased supervised exercise until they reached the assigned energy level.)
6. The exercise groups participated in 3 to 4 fitness training sessions each week with a training intensity at the heart rate associated with 50% of each woman's peak oxygen consumption (VO2 in liters per minute).
7. All exercise groups continued to participate in the laboratory supervised exercise sessions 3 or 4 times a week for 6 months.
8. All participants continued their usual activities (except for the training periods) during the week. All wore a pedometer during this period to measure steps per day.
9. Primary outcome = change in fitness as measured by the peak VO2 (liters per minute) in response to the 3

exercise levels, compared with the no-exercise groups.

RESULTS

1. Mean baseline absolute VO2 values = 1.3 L/min
2. Mean minutes of exercise per week: 4 kcal/kg/week = 72; 8 kcal/kg/week = 139; 12 kcal/kg/week = 192.
3. At 6 months, the exercise groups increased their absolute VO2 compared with the no-exercise group: 4 kcal/kg/week +4.2%; 8 kcal/kg/week +6.0%; 12 kcal/kg/week +8.2% (a training effect).
4. As determined by pedometer during the week, all groups continued to take about the same number of steps per week as at baseline, with no difference between groups after the first month.
5. No statistically significant changes in BP, weight, or cardiovascular disease risk factors over 6 months. Waist circumference was significantly smaller in all 3 exercise groups.

DISCUSSION

1. The primary finding of the trial: A controlled exercise program in postmenopausal women resulted in a dose-response increase in fitness. Women who exercised 3 or 4 times a week increased their fitness in proportion to the amount of energy expended during the exercise sessions.
2. "Perhaps the most striking finding of our study is that even activity at the 4-kcal/kg/week level (approximately 72 minutes pre week) was associated with a significant improvement in fitness compared with women in the non-exercise group."
3. The improvements in fitness occurred at a modest training intensity (heart rate at 50% of peak VO2), and occurred during the lifetime when fitness is usually decreasing.
4. For many years the focus was on vigorous activity conducted within an exercise training model. In the 1990s the view began to change with the development of NIH consensus recommendations (at least 30 minutes a day of moderate intensity activity most days of the week). Recent reports emphasize the need for physical activity of 60 minutes or more a day to prevent weight gain or re-gain after weight loss.
5. But, as demonstrated in this study, even as little as one hour and 12 minutes of moderate-intensity activity a week accumulated over 3 days had a significant effect on fitness. This may be a practical application in individuals who cannot or do not take more time to exercise.
6. As demonstrated by pedometer readings, there was no change in activity other than that of the supervised exercise sessions. This suggests that the observed effects of supervised exercise were a result of the program and not changes in physical activities of daily living.
7. There was no change in weight or body fat percentage in the study. This was expected because participants were informed that the objective was not weight loss. They were encouraged to maintain their baseline lifestyle habits.
8. There was a reduction in waist circumference in all 3 exercise groups. This confirms other observations that exercise is an effective tool for reducing waist circumference even if there is no weight loss.
9. The purpose of the study was primarily to evaluate exercise dose-response. It was conducted in near ideal circumstances.

CONCLUSION

Previously sedentary, overweight, or obese postmenopausal women experienced a graded dose-response in fitness across levels of exercise training. Even modest exercise for little over an hour a week had a training effect.

JAMA May 16, 2007; 297: 2081-91 Original investigation, The Dose-Response to Exercise in postmenopausal Women (DREW) study, first author Timothy S Church Louisiana State University System, Baton Rouge

An editorial in this issue of JAMA by I-Min Lee, Harvard Medical School, Boston Mass, comments and expands:

Physicians typically start with a dose of a drug believed to be the minimum effective dose. If the patient does not respond, this initial dose may then be titrated upward to a maximum dose beyond which adverse effects of the drug are unacceptable.

Physical activity can behave like a drug in this respect. It is plausible that there is a minimum dose of physical activity for health benefits, and beyond a certain dose there is a risk of adverse effects (eg, musculo-skeletal injuries, and even sudden death).

The minimum dose, the dose response, and maximum safe dose of physical activity are not well understood. Dose questions related to physical activity are not just fodder for academic rumination. Dose has practical applications.

Over the years various expert groups have formulated different physical activity recommendations and guidelines. "Predictably, many patients and clinicians are confused about what dose of physical activity is needed."

The above study provides some clarification. Physical fitness showed a linear dose-response over 3 exercise groups. Peak oxygen consumption (a marker of fitness) increased as intensity and duration of exercise sessions increased. Even subjects exercising at 50% of recommendations for a little over an hour a week experienced some improvement in fitness.

These results agree with data from the Women's Health Study 2001, which reported effects on fitness of walking 1 to 1.5 hours a week. Women who did so had half the risk of developing coronary heart disease as did sedentary women. "An achievable dose of physical activity may be sufficient to begin reaping health benefits."

"Even a little is good; more may be better."

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Surgery Should Not Be Performed If Systematic Follow-Up Is Not Available

5-10 BARIATRIC SURGERY FOR MORBID OBESITY

About one quarter of all adults in the US are obese (BMI of 30 or more). About 5% are extremely or morbidly obese (BMI 40 or more).

Obesity, especially abdominal obesity, is associated with increased risks of hypertension, diabetes, dyslipidemia, sleep apnea, coronary heart disease, and stroke.

The pathophysiology of obesity is complex, and poorly understood. It includes genetic, behavioral, psychological, and other factors. Heredity may explain some of the population variance in BMI. Declining physical activity, and increased consumption of energy-dense foods play a role. (*A development of "civilization.")* Bariatric surgery reduces caloric intake by modifying the anatomy of the g.i. tract. Operations are classified as restrictive or malabsorptive. Restrictive procedures limit intake by creating a small gastric reservoir with a narrow

outlet to delay emptying. Malabsorptive procedures bypass portions of the small intestine, reducing nutrient absorption. All procedures maintain the normal pancreatic and biliary secretions. (*See page 2179 for illustrations*.) The changing popularity of specific surgical procedures over time suggests that the ideal procedure has not been established. Laparoscopic procedures are available.

No large, randomized trials have compared current bariatric techniques with medical management of severe obesity. Summary assessments suggest a typical weight loss of 44 to 110 pounds with various surgical procedures as compared with modest weight *gain* in medically treated patients. One large trial reported a 23% weight loss vs a 0.1% gain at 2 years, and a 16% weight loss at 10 years vs a 1.6% gain. Another study reported a mean decrease in BMI from 50 to 33 at 2 years.

Conditions associated with obesity consistently improve after surgery. (Eg, 77% of patients with type 2 diabetes no longer required medications after surgery.) Improvements continued after 10 years.

A consensus conference of the NIH (1991) recommended criteria for bariatric surgery:

BMI 40 or greater

BMI 35-40 for patients with a high risk condition

Failure of medical therapy

Absence of medical or psychological contraindications

Patients must understand the risks of the procedure, and have a strong motivation to comply with the post-surgical regimen.

Thorough medical evaluation is required prior to surgery. The psychological evaluation of candidates for surgery is one of the most important and difficult elements of the clinical assessment. Most patients presenting for surgery have one or more psychiatric disorders.

Patients undergoing surgery often believe they will lose more weight than is consistent with clinical experience. And may think that minimal personal effort or risk is involved.

Perioperative care requires specialized expertise and facilities. Choosing surgeons and hospitals that have great experience is essential.

A comprehensive plan for long-term care is necessary. Surgery should not be performed if systematic follow-up is not available, and should not be planned until the patient has made a commitment to participate in such care.

Adverse effects include a mortality rate up to 2%, and many perioperative complications. Postoperative complications are common: nausea and vomiting (~50%); dumping syndrome[1], deficiencies of protein, vitamins, iron, calcium, and other nutrients as a component of malabsorption. All require monitoring and replacement. Patients may require readmission or re-operation.

NEJM May 24, 2007; 356: 2176-83 “Clinical Therapeutics”, review article by Eric J DeMaria, Duke University Medical Center, Durham, NC.

1 I have not thought about, or read about, the dumping syndrome since the days of vagotomy and drainage procedures for peptic ulcer disease. It consists of a series of vasomotor and gastrointestinal signs and symptoms (abdominal discomfort, nausea, diarrhea, belching, tachycardia, palpitations, diaphoresis, light-headedness, and rarely syncope). Symptoms may occur within 30 minutes after a meal likely due to rapid emptying of hyperosmolar gastric contents into the small intestine, resulting

in a fluid shift into the gut lumen with plasma volume contraction, and acute intestinal distention. Release of vasoactive gastrointestinal hormones may play a part. Late symptoms (2 to 3 hours p.c.) may be due to hypoglycemia secondary to excessive insulin release. (From Harrison's Principles of Internal Medicine 15th edition.)

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5-11 ONCE-YEARLY ZOLEDRONIC ACID FOR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Bisphosphonates (eg, *orally* administered alendronate and risedronate) inhibit osteoclast-mediated bone resorption and reduce risk of fracture in women with osteoporosis.

A single *intravenous* infusion of zoledronic acid (**ZA**; a bisphosphonate) decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis.

This study assessed the effects of annual infusions of ZA on fracture risk over a 3-year period.

Conclusion: Once-yearly infusions reduced the risk of vertebral, hip, and other fractures.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 3800 postmenopausal patients (mean age = 73). All had a bone mineral density T-score of -2.5 or less (*osteoporosis*) at the femoral neck, with or without existing vertebral fracture, or a T-score of – 1.5 or less (*osteopenia*) with evidence of at least 2 mild vertebral fractures or one moderate vertebral fracture.
2. Randomized to: 1) ZA (5 mg) given i.v. as a single dose over 15 min, or 2) Placebo i.v.
3. Both were given at baseline, at 1 and at 2 years. In addition, all patients received oral daily calcium (1000 to 1500 mg), and vitamin D (400 to 1200 IU).
4. Primary endpoints = new vertebral and hip fracture determined by repeat radiographs. Followed-up for 3 years.

RESULTS

1. Treatment with ZA reduced the risk of fracture during 3 years

	ZA	Placebo	Absolute difference	NNT*
Vertebral fracture	3.3%	10.9%	7.6%	14
Hip fracture	1.4%	2.5%	1.1%	91

(* = number of patients needed to treat to prevent one fracture.)

2. Other fractures were also reduced
3. In the ZA group, bone mineral density increased as compared with the placebo group. Biochemical markers of bone turnover decreased.
4. Adverse effects:

Post-dose symptoms occurred more commonly in the ZA group than in the placebo group:

Transient slight increase in serum creatinine.

Chills, fever, myalgia, flu-like symptoms, headache, arthralgia, nausea, bone pain, back pain.

(6% for placebo vs 16% for ZA.)

Atrial fibrillation (0.5% for placebo vs 1.3% for ZA)

Drop in serum calcium (1 patient for placebo vs 49 patients for ZA).

Slight transient increase in inflammatory ocular adverse events, chiefly conjunctivitis

DISCUSSION

1. During a 3-year period, annual infusions of ZA reduced the risk of fractures at all key osteoporotic fracture sites. The reduction in vertebral fracture rate was greater than the rate reported for oral bisphosphonates. All other prospectively defined categories of fracture were also reduced.
2. A regimen of infusions once a year appears to ensure that patients will have a full treatment effect for at least 12 months.
3. The effect on biochemical markers was similar to that of oral bisphosphonates.
4. Mild to moderate post-dose symptoms occurred most commonly after the first infusion. The symptoms typically resolved within 3 days.
5. Most of the increased risk of atrial fibrillation was observed more than 30 days after the infusion, a time when ZA is undetectable in the circulation. The biological mechanisms are not known.
6. The once-yearly treatment might improve compliance as compared with the weekly or monthly regimen of oral bisphosphonates.[1]

CONCLUSION

A once-yearly infusion of ZA during a 3-year period was associated with a sustained reduction in risk of fractures. “In addition, the treatment had a favorable safety profile and was generally well tolerated.”[2]

NEJM May 3, 2007; 356: 1809-22 Original investigation by The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) Pivotal Fracture Trial, first author Dennis M Black, University of California, San Francisco

Study supported by Novartis Pharma

1 I believe this comment about improved compliance is a stretch. Taking one oral tablet a month with water and remaining upright for 30 minutes is not much of a burden considering that adverse effects are nil with this program. The adverse effects of ZA would discourage many women. However, this is a personal choice.

2 Also a stretch.

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