INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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We begin this issue with an examination of some disturbing aspects of the move underway in the U.S. and Canada to vaccinate all girls age 11-12 against the human papillomavirus and to attempt to have the vaccination made mandatory for school attendance. While this matter has been in the news lately, there are some aspects of which readers of this Newsletter may not be aware.

Also discussed is the association between folic acid intake and both stroke and colorectal cancer. The two studies discussed not only suggest that caution is in order regarding the amount of synthetic folic acid that it is wise to consume since at least for cancer, this chemical may have both preventive and promoting properties. Other studies are mentioned which also highlight this very important issue of overdosing with folic acid from pills or fortified food. Also, these folic acid studies again raise the issue of unmetabolized folic acid in the circulation when large amounts of the synthetic chemical are ingested.

Three very recent studies highlighting the importance of whole grains rather than refined grains in the context of various health issues are presented. While most readers of the Newsletter are aware of the importance of whole grains, these studies provide impressive evidence of the broad health issues involved.

Studies on the importance of vitamin D continue to appear frequently in the medical literature. Some readers may feel inundated with information on this subject. In your editor's humble opinion, vitamin D is destined to become the undisputed hero micronutrient of this decade. This month we discuss the importance of this vitamin in the context of age related macular degeneration and review briefly the first randomized placebo controlled intervention trial (mainstream medicine's so-called Gold Standard) of vitamin D carried out in order to investigate its role in overall cancer prevention. This latter study is particularly interesting because it further helps to establish the serum levels of the standard vitamin D marker that are associated with significant risk reduction for cancer.

And last, but not least, Hans Larsen, familiar to most readers as founder and publisher of International Health News and the editor of this newsletter for many years, has provided an excellent and important review on the prevention of osteoporosis which will appear in two parts starting with this issue.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at *http://www.yourhealthbase.com/vitamins.htm*.

Wishing you continuing good health,

William R. Ware, PhD, Editor

Highlights

VACCINATE ALL 11-12 YEAR OLD GIRLS AGAINST HPV???

Vaccination for several variants of the human papillomavirus (HPV) is underway with Merck's new vaccine Gardasil. The approval of Gardasil has been greeted by mainstream medicine with unbridled enthusiasm, as indicated by journal articles with titles such as *HPV Vaccine: A Cornerstone of Female Health* and *HPV Vaccination with Gardasil: A Breakthrough in Women's Health.* Another drug company has a similar vaccine in the approval stage. Merck's marketing campaign included attempts to have HPV vaccination made mandatory for school attendance in as many states as possible, a move which understandably raised considerable vocal opposition. However, at least in some states, the adopted or proposed legislation allows parents to opt out for reasons much more general than acceptable in the case of the common mandated vaccinations. In January the American Academy of Pediatrics and the Association of American Physicians and Surgeons, among others, raised concerns of the absence of safety data in the target population (girls age 11-12) and the wisdom of immunizing girls against a disease that is now less prevalent in the US and that does not develop until later in life, (i.e. will the immunity last?). Thus parents, especially those with daughters in the targeted age group need information on which to base their decision, information which is not biased by the huge commercial interest involved. This is not easy, since there are many unanswered questions and issues.

In the April issue of *The Journal of Family Practice*, Dr. Joseph De Soto raises some concerns:

- There is no evidence that Gardasil is effective after 5 years
- It is unknown whether this vaccine will cause autoimmune and neurological problems in the long term.
- The risk of pelvic inflammatory disease, appendicitis and gastroenteritis is at least doubled.
- The vaccine has not been adequately tested in girls under age 16.

There are other issues not discussed by Dr. De Soto. Gardasil apparently is ineffective in individuals already infected by HPV, and thus, given that some 11-12 year old girls are already sexually active, a fraction of those in the suggested target group would be given presumably ineffective prophylactic vaccination. Also, cervical cancer takes years to develop, which means that studies of the vaccine' effectiveness required a surrogate endpoint, in this case advanced cervical intraepithelial neoplasia (CIN), a recognized precancerous condition. Thus the ability of the vaccine to actually prevent cervical cancer 10-20 years down the road has not and probably cannot be demonstrated. In addition, since the vaccine does not target all variants of the HPV virus, vaccination does not eliminate the need for continued screening as is already recommended. Critics also point out that when screening reveals CIN, it in general is successfully treated, which brings into question the need for a vaccine in countries where periodic screening is widely used and CIN promptly treated.

As regards side effects, a public interest organization (Judicial Watch) recently obtained adverse reaction data from the FDA by using the Freedom of Information Act. Three deaths attributed to heart problems and/or blood clotting were possibly associated with the vaccine. Also, of 42 women who received the vaccine while pregnant, 18 experienced side effects ranging from spontaneous abortion to fetal abnormalities. Other side effects include paralysis, Bell's palsy, Guillian-Barr syndrome and seizures (see the website cited below for more details and links to source material.

Editorial: Flogging Gardasil. ***Nature Biotechnology****, 2007, Vol. 25, No. 3, pp. 261.*

De Soto, J. Should HPV Vaccination be Mandatory? ***Journal of Family*** *Practice, 2007, Vol. 56, No. 4, pp. 267-8*
Gross, G. HPV-Vaccination Against Cervical Carcinoma: Will it Really Work? ***Medical Microbiology and Immunology****,2007, Vol 196, pp. 121-5.*
Baden, L. R. et al. Human Papillomavirus Vaccine—Opportunities and Challenge, ***New England Journal of Medicine,*** *2007, Vol. 359, pp. 1900.*
Sawaya, G. F. HPV vaccination—More answers, More Questions, ibid pp. 1991.
Judicial Watch
www.judicialwatch.org/printer_6299.shtml).

FOLIC ACID – A DOUBLE EDGED SWORD??

FOLIC ACID, HOMOCYSTEINE AND STROKE PREVENTION

Numerous studies provide evidence that homocysteine may be a modifiable risk factor for cardiovascular disease. Epidemiologic studies show an independent and graded association between homocysteine serum levels and cardiovascular risk. Thus there have been a number of studies which attempted to address the obvious question: will the reduction of homocysteine levels using folic acid with or without other B-vitamins reduce the risk of cardiovascular disease or related adverse events.

A recently published meta-analysis (study of pooled results from a number of studies in an attempt to improve the statistical power) examined the effect of lowering homocysteine levels using folic acid supplementation with the aim of stroke prevention. The eight studies included in the meta-analysis involved participants with pre-existing diseases such as coronary heart disease, stroke or end-stage renal disease. Overall, folic acid supplementation with or without B6 and B12 resulted in an 18% decrease in stroke risk. When the duration of intervention exceeded 36 months, the decreased risk was 29% whereas for shorter interventions there was no significant effect. For homocysteine lowering of 20% or more, the reduced risk was 23% but for smaller reductions, there was no effect. Only in studies conducted in countries where there was no grain fortification were significant risk reductions found (25%) and when the results were stratified by history of just stroke, only the absence of stroke produced reduced risk from supplementation (25%). The authors point out that this last result is consistent with an earlier meta-analysis where a 24% risk reduction for stroke was found when a study involving stroke patients was excluded from the analysis. The authors conclude that folic acid supplementation can effectively reduce the risk of stroke in the setting of primary prevention.

Wang, X. et al. Efficacy of Folic Acid Supplementation in Stroke Prevention: a Meta-Analysis. ***The Lancet,*** *Vol. 369, pp 1876.*

Editor's comments: This meta-analysis relates to primary prevention only in the sense that the participants who benefited had no history of stroke. Thus stroke may be an exception to the disappointing results of a number of trials. In the meta-analysis of Bazzano *et al* (JAMA 2006;296:2720-26) folic acid supplementation was found to be ineffective in reducing the risk of cardiovascular disease including stroke or all-cause mortality among participants with a prior history of vascular disease. Some of the individual studies even suggested the intervention produced increased risk, especially of events associated with coronary heart disease. As Joseph Loscalzo points out in an editorial (N Engl J Med 2006;354:15), "The straightforward but incorrect view that folic acid can decrease homocysteine levels and, thus, reduce the risk of atherosclerosis effectively may be an unintended consequence of oversimplifying a complicated metabolic network." It is now suspected that the homocysteine lowering power of folic acid may be opposed by adverse changes in biochemistry due to high levels of folic acid that counterbalance the theoretical benefits or even increase risk.

Also, there is the unresolved problem that the intake of synthetic folic acid, the inexpensive and readily available form used in both supplements and fortification, when it exceeds a low level of about 200-400 micrograms, produces unmetabolized folic acid in the circulation and the levels can become quite large with high intakes. Unfortunately, no one knows if these levels present a long-term danger. But what is clear is that individuals who take a multivitamin and in addition consume fortified foods such as cereals and bread can have intakes synthetic folic acid between 800 and 1500 micrograms per day. Therapeutic doses of up to 5000 micrograms/day are commonly prescribed

(Sweeney, M.R. *et al*, BMC Public Health 2007;7:41). Studies typically use 1 to 5 mg per day.

Nevertheless, the risk reductions found by Wang *et al* are sufficiently impressive to warrant attention and individuals concerned about primary stroke prevention need to examine their intake of folic acid, B6 and B12. A multivitamin containing these components with folic acid at not more than 400 micrograms per day would seem consistent with the threshold for enhanced risk although if large amounts of fortified food are consumed, even this may be too much, especially when one considers the following report on colorectal cancer.

FOLIC ACID AND PREVENTION OF COLORECTAL CANCER

There are a large number of epidemiologic studies that have shown benefit from higher folate status and intake of both folate and folic acid and as well higher intakes of fruits and vegetables in the context of primary prevention and decreased risk of colorectal polyps and colorectal cancer (CRC). Most of these studies were performed before mandatory folic acid fortification in the U.S. (1998) and before heavy use of supplements became popular, especially among the older segment of the population. One of the important questions under study involves the effect of folic acid supplementation on the recurrence of colorectal adenomas (polyps). With the growing popularity of colonoscopies as a preventive strategy, there are an ever-increasing number of individuals who have had polyps removed and who are obviously concerned about recurrence. Polyps are viewed as precursors to CRC. A major study by the Polyp Prevention Study Group has just reported and the results are both interesting and disturbing.

The study in question was a randomized intervention trial using 1 mg/day of synthetic folic acid. Participants all had a recent history of surgically removed colorectal adenomas and no previous large intestine cancer. Follow-up consisted of two colonoscopies, one after three years and a second 3-5 years later. The criteria for entry into the study meant that the group involved was at high risk for recurrence and thus this study addressed the issue of secondary, not primary prevention. The unexpected result was that folic acid at 1 mg/day did not reduce the risk of recurrent colorectal adenomas. In addition, this intervention was associated with a higher risk of having 3 or more new adenomas and also a higher risk of non-CRC cancer. The authors discuss the biological plausibility of folic acid/folate acting both as an inhibitor and promoter of CRC, depending on the stage of the disease at exposure, and there are a number of studies suggesting that the same phenomenon may operate in other types of cancer. This is clearly an area needing much more research

In an accompanying editorial, Ulrich and Potter from the Fred Hutchison Cancer Research Center point out that this study provides no information on either true primary prevention or on the effect of folic acid supplementation on individuals with unresected colorectal polyps. The latter question is of particular relevance given that among patients with resected adenoma, the folic acid dose used was not beneficial and may have increased the risk of multiple polyp recurrence. Thus the question—do high levels of folic acid intake increase the progression of existing polyps into full-blown CRC? But this question cannot be ethically studied and one is left with uncertainty and guidance that will be limited to animal studies and mathematical models. With regard to the unexpected nature of the results, the editorialists appear to favor an explanation that involves the dual role of folate in carcinogenesis. By preventing DNA damage, folate may provide primary protection, but once pre-neoplastic lesions are present, folate favors rapidly proliferating tissues, including tumors, and benefit switches to increased risk.

Cole, B.F. et al. Folic Acid for the Prevention of Colorectal Adenomas: A Randomized Clinical Trial. ***Journal of the American Medical Association****, 2007, Vol. 297, pp. 2351.*

Ulrich, C.M. and Potter, J.D. Folate And Cancer—Timing is Everything. Ibid, pp. 2408.

Ulrich, C.M. and Potter, J.D. Folate Supplementation: Too Much of a Good Thing? ***Cancer Epidemiological Biomarkers and Prevention****, 2006, Vol. 15, pp. 189-93.*

Kim, Y-I. Folate: a Magic Bullet or a Double-edged Sword for Colorectal Cancer Prevention? ***Gut,*** *2006, Vol. 55, pp. 1387-9.*

Editor's comments: The reader is referred to the IHN Research Review on Breast Cancer Prevention for a discussion of high levels of folic acid and enhanced risk this disease. Also a study just published by Lawson *et al* (J Natl Cancer Inst 2007;99:754-64) found significantly enhanced risks of prostate cancer, both total and localized, in individuals who had high intakes of folic acid. Unfortunately, the problem discussed above of unmetabolized circulating folic acid has received little attention in this context and essentially nothing is known about its potential role in carcinogenesis. However, in the colorectal cancer study, individuals

taking a multivitamin were not excluded, and this U.S. based study overlapped with the advent of fortification. Thus participants could have had a total folate/folic acid daily intake of well over the administered 1000 micrograms with totals up to 2000 micrograms or more possible. This would result in huge levels of unmetabolized serum folic acid with totally unknown ramifications. There is urgent need for studies of the potential role of unmetabolized folic acid, a synthetic chemical unknown to evolutionary human biochemistry, in connection with the possible cancer promoting properties of high levels of folic acid intake, especially in situations where cancer at some stage of development is already present. Indeed, it seems reasonable to assume that many individuals have early stage cancer and are totally unaware of its presence.

Until all the issues raise here are resolved, great care appears necessary with regard to total folate/folic acid intake, especially in the U.S. and Canada where food fortification is mandatory. At the risk of stating the obvious, maintaining adequate folate status principally from food appears to be highly desirable. The chief dietary sources according to a U.S. government website are approximately as follows:

- Beef liver, cooked, braised, 3 oz — 185 micrograms
- Cowpeas, immature, cooked, boiled, 1/2 cup — 105 micrograms
- Spinach, frozen, cooked, boiled, 1/2 cup — 100 micrograms
- Great northern beans, boiled, 1/2 cup — 90 micrograms
- Asparagus, boiled, 4 spears — 85 micrograms
- Vegetarian baked beans, canned, 1 cup — 60 micrograms
- Spinach, raw, 1 cup — 60 micrograms
- Green peas, frozen, boiled, 1/2 cup — 50 micrograms
- Broccoli, chopped, frozen, cooked, 1/2 cup — 50 micrograms
- Avocado, raw, 1/2 cup — 45 micrograms
- Romaine lettuce, 1/2 cup — 40 micrograms

Citrus fruits and some other fruits are fair sources, with amounts per serving up to 50 micrograms depending of amount consumed. Source: http://ods.od.nih.gov/factsheets/folate.asp

It is hoped that these figures properly reflect the decrease in folate associated with cooking. Omitted from this list are fortified foods, the point being to emphasize sources of natural folate rather than synthetic folic acid. Note that some juices and so-called health bars are heavily fortified with folic acid.

Obviously, the natural folate-rich foods are limited and some are not, to say the least, universally fancied. Studies that have examined natural folate intake typically find amounts of 100 to 200 micrograms, amounts which are not surprising. If the optimum is indeed 400-500 micrograms, then some supplementation is in general indicated. At issue here is not bringing up the total intake to 400-500 micrograms with the modest amounts of the synthetic vitamin, but considering avoiding high intakes, intakes which can occur almost unnoticed by taking multivitamins and consuming fortified milk, juices, cereals and other grain products. One serving (3/4 cup) of a fortified breakfast cereal typically provides about 400 micrograms, and there is some evidence that the fortification is not well controlled and the amounts can be even higher. Typical multivitamin pills provide a total of 800 micrograms if two are taken. The so-called B-50 preparation contains 1 mg per pill of folic acid. The bottom line is that no one knows the risk associated with high circulating levels of unmetabolized, synthetic folic acid, a chemical foreign to human biochemistry, and in fact the answer may never be known. Some cancers take a long time to develop and in addition, there are ethical problems with many studies that would have the potential of offering useful information. Finally, natural folate is not available as a supplement.

MORE EVIDENCE OF THE IMPORTANCE OF WHOLE-GRAINS

Whole-grains would have never become an issue if industrial methods had not been developed at the end of the 19th century which effectively removed most micronutrients and fiber from cereal grains leaving mainly a dietary source of starch which some critics of modern diets like to equate to simply

eating sugar. This phenomenon has been long recognized and the health conscious have traditionally sought out cereal grain products made from whole-grains, although knowledge was necessary to avoid faux whole grain products passed off as the real thing, the common so-called whole wheat bread being a good example. Three studies have very recently been reported in the *American Journal of Clinical Nutrition* that reinforce the view that whole-grains are very important.

The first study by Mellen *et al* involved a 5-year follow-up designed to measure the progression of atherosclerosis in a multiethnic population with a mean age of 55 years. Presence and progression of atherosclerosis was measured by the carotid intimal medial thickness evaluated by ultrasonically examining the carotid arteries (arteries that run on each side of the neck). Whole grain intake was measured by a questionnaire and included dark bread, high-fiber bran or granola cereals, shredded wheat, oatmeal, cream of wheat and grits. Whole grain foods were found to provide benefit in terms of progression of atherosclerosis which was not attributable to individual risk factors, single nutrient constituents or dietary patterns.

The second study was based on data from the Iowa Woman's Health Study and focused on the role of whole-grains in non-cardiovascular, non-cancer mortality attributed to inflammatory diseases. Postmenopausal women aged 55-69 were evaluated at baseline and followed for 17 years. Whole-grains were defined as dark bread, cold whole-grain breakfast cereal (≥ 25% by weight of whole grain or bran), brown rice, popcorn, wheat germ, bran, cooked oatmeal and other grains. When the lowest fifth in terms of whole grain intake was compared to the highest fifth, a risk reduction in mortality attributed to non-cardiovascular, non-cancer inflammatory diseases was 34% and intake above about 4 servings per week was found to be protective. These results were extensively adjusted for confounding factors. Interestingly enough, significant benefit was also seen in total mortality, cardiovascular deaths and coronary heart disease mortality when the lowest vs. the highest quintiles were compared.

The third study by Schatzkin *et al* looked at the relationship between whole-grain intake and colorectal cancer. Approximately 300,00 men and 200,000 women were evaluated with a questionnaire at baseline and followed for 5 years. Whole-grains were defined as ready-to-eat cereals, high-fiber cereals, other fiber cereals, whole grain breads or dinner rolls, cooked oatmeal or grits, and popcorn. The questionnaire also contained a number of items made from refined grains such as cookies and chips. When the results were analyzed for the influence of fiber, no significant association was found. This is consistent with most other studies even though it is counter intuitive. Whole grain intake was found to offer significant protection from colorectal cancer in men even when the results were subjected to an analysis to remove confounding factors. The association was stronger for rectal than for colon cancer. These results reinforce earlier studies which also found a protective effect of whole-grains on the incidence of colorectal cancer.

Mellen P.B. et al. Whole-grain Intake and Carotid Artery Atherosclerosis in a Multiethnic Cohort: The Insulin Resistance Atherosclerosis Study. ***American Journal of Clinical Nutrition****, 2007, Vol. 85, pp. 1495-502,*

Jacobs, D.R., et al. Whole-grain Consumption is Associated with a Reduced Risk of Non-cardiovascular, Non-cancer Death Attributed to Inflammatory Diseases in the Iowa Women's Health Study. ibid, pp. 1602-14.

Schatzkin, A. et al. Dietary Fiber and Whole-grain Consumption in Relation to Colorectal Cancer in the NIH-AARP Diet and Health Study. ibid, pp. 1353-60.

Editor's comments: No one appears to have pinpointed the actual constituents in whole-grains that confer the above benefits as well as other benefits described in the literature including diabetes prevention. Whole-grains consist of endosperm, bran and germ layers, and it is the latter two that are removed by refining. Bran and the germ layers are nutritionally rich and complex and contain both soluble and insoluble fiber, antioxidants, minerals, and a number of phytonutrients. Which whole-grain sources offer the greatest benefit in the context of the three above studies is unknown but the message seems clear, eat lots of foods containing minimally refined whole-grains and avoid as much as possible meeting ones energy intake requirements with foods made from refined grains, even though they are much more readily available and may have greater taste appeal for some individuals. Even mainstream nutrition has adopted a similar recommendation.

NEWS BRIEFS

DIABETES AND STROKE RISK

A recent large study examined the short-term risk of stroke in newly treated diabetics as compared to persons free of diabetes. Over 12,000 subjects, 55% male, were in the diabetes group identified from Saskatchewan provincial health care system records by a first prescription for an oral anti-diabetic drug. The incidence of stroke was determined from the same database. It was found that over a 5-year follow-up, newly treated diabetics had almost twice the incidence of stroke compared to the general population. The risk by age was 80% greater for age > 75 and 460% greater for the 30- to 44-year age category. The authors point to the obvious need for cardiovascular risk management in newly treated diabetics.

Jeerakathil, T. et al. Short-Term risk for Stroke is Doubled in Persons with Newly Treated Type 2 Diabetes Compared with Persons without Diabetes. ***Stroke****, 2007, Vol. 38, pp. 1739-43.*

Editor's comment: The population of newly diagnosed diabetics is probably considerably larger than those actually receiving initial pharmaceutical treatment, and these results presumably apply to this group as well, although there is always the possibility, made more plausible by recent items featured by the media, that the drug treatment for diabetes increased the risk of stroke. It is also worth remarking that strokes can be vastly more devastating in terms of quality of life than heart attacks that are survived with minimal long-term adverse effects and this should motivate individuals to be particularly aggressive in endeavoring to reduce the risk of stroke. Readers interested in an up-to-date and through discussion of this subject are referred to the book *Thrombosis and Stroke Prevention, Second Edition* by Hans Larsen which can be ordered from the IHN website.

VITAMIN D AND THE RISK OF MACULAR DEGENERATION

Macular degeneration is far from uncommon in aging populations and has a huge impact on the quality of life since the resultant impaired vision generally makes it difficult to read, and as the disease progresses, dangerous to drive. Parekh *et al* have recently examined the association between age-related macular degeneration (AMD) and vitamin D status by mining data from a large U.S. government database (NHANES II). Over 11,000 individuals aged 40 and older were involved. Vitamin D status was determined by 25 hydroxyvitamin D serum levels. The risk reduction for early onset AMD among participants in the highest vs. the lowest fifths of serum vitamin D status was a statistically significant 36%. Dietary intakes of vitamin D from either fish or milk were also significant either for early or advanced AMD. For individuals who did not consume milk daily, the reduced risk associated with taking vitamin D through supplements vs. no supplements was 33%. When the risk of early AMD was studied according to serum 25 hydroxyvitamin D levels, the trend with increasing level was highly significant with a 40% reduction at levels > 78 nmol/L, a level around the currently suggested but unofficial minimum level for optimum health.

Parekh, N. Association Between Vitamin D and Age-related Macular Degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. ***Archives of Ophthalmology****, 2007, Vol. 125, pp. 661-9*

VITAMIN D STATUS AND OVERALL CANCER RISK

The first randomized controlled trial with an endpoint of cancer of all types and an intervention sufficient to raise serum 25-hydroxyvitamin D levels to > 80 nmol/L has just been reported. This was a 4-year double-blind study of 1179 healthy postmenopausal women aged >55 years in rural Nebraska. Subjects were randomized to receive 1400-1500 mg of calcium alone, or calcium plus 1100 IU of vitamin D3 per day or a placebo. The decrease in relative risk of cancer in the Ca + D group was about 60%. as compared to the placebo group. For cancers diagnosed after 12 months, the reduction in relative risk in the Ca + D group increased to about 77%. In terms of absolute risk reduction, in the period from year 2 to 4, approximately 98% of the D + Ca group remained cancer free whereas this was only true for 93% of the placebo group. The serum level of 25-hydroxyvitamin D was a significant independent predictor of cancer risk. The specific cancers monitored included breast, colon, lung, lymph (leukemia, myeloma), uterus with all others lumped in one "other" category. The authors point out that these results highlight the importance of promoting optimum vitamin D status and emphasize the importance of achieving and maintaining a high serum 25-hydroxyvitamin D level.

Lappe, J. M. et al. Vitamin D and Calcium Supplementation Reduces Cancer Risk: Results of

a Randomized Trial. ***American Journal of Clinical Nutrition****, 2007, Vol. 85, pp. 1586-91*

Editor's comments*:* At baseline the mean 25-hydroxyvitamin D level in this cohort was about 72 nmol/L. At 12 months supplementation with 1100 IU/day of vitamin D3 raised mean serum levels to 96 nmol/L. It is this change that produced the large risk reductions in all cause cancer in the study of Lappe *et al,* and it must be admitted that these risk reductions, when added to those already reported in this Newsletter specifically for breast and colorectal cancer, are dramatic and compelling. As has been pointed out a number of times in this Newsletter, a routine blood test is available for this vitamin D metabolite. It is a pity that it is not part of the commonly ordered blood tests at periodic physical exams. It can be argued that it might be one of the most important health parameters to measure both in the spring and fall, and that by now, considerable data exists on optimum levels, information which incidentally is not contained on the clinical laboratory printouts which describe the "normal" range. Achieving optimum levels appears as simple as picking up a bottle of vitamin D3 from the drug store and taking enough to bring the serum level up to 95-100 ng/mol. If Vitamin D3 was a prescription drug, it can almost be guaranteed that it would be aggressively and no doubt successfully marketed by the patent holder(s), in doctors' offices and on prime time TV. The simplicity of vitamin D supplementation as compared to other approaches to cancer prevention is striking and the accumulated data compelling.

COCOA REDUCES BLOOD PRESSURE

In a study just published, German researches from the University Hospital in Cologne report research aimed at determining the association between chocolate intake and blood pressure. Volunteers of both genders between the ages of 55 and 75 years with either upper-range pre-hypertension (130/85 to 139/89) and stage 1 hypertension (140/90 to 160/100) but otherwise healthy with normal serum lipid and glucose levels were given about 6 grams of dark chocolate per day for 18 weeks. When compared to controls who were given white chocolate, mean systolic BP decreased by almost 3 mm Hg and diastolic by almost 2 mm Hg. The decline was greater, the greater the baseline BP but the study was not of sufficient length to identify a leveling off of the beneficial effect. The authors point out that while these are modest changes, a 3 mm Hg reduction in systolic BP would be expected to reduce the risk of stroke mortality by 8% and decrease coronary heart mortality by 5%. Furthermore, they point out that in a recently published study in elderly men, just 4.2 g of cocoa per day resulted in about a 50% reduction in cardiovascular or all-cause mortality, suggesting that some component or components in chocolate may have cardio protective properties that go beyond BP reduction. Participants experienced no changes in weight, or lipid or glucose plasma levels during the study.

Taubert, D. et al. Effects of Low Habitual Coco Intake on Blood Pressure and Bioactive Nitric Oxide. ***Journal of the American Medical Association,*** *2007, Vol. 298, pp. 49-60.*

Editor's comments: It is unfortunate that this study was not carried on long enough to determine when the beneficial effect leveled off and in addition, to determine if there was a dose dependence. Thus the benefits for long-term use may be even greater. If one can accurately measure blood pressure at home, this might appear to be an easy experiment to attempt to reproduce and extend. However, BP can vary throughout the day, is dependent on the length of rest prior to the measurement, and can vary with the elevation of the arm relative to the level of the heart. If the method that employs a stethoscope rather than an automated device is used, good hearing and careful reduction of the cuff pressure is necessary to accurately determine the diastolic and systolic pressure. Thus small changes are not that easy to measure. In the above study, three measurements were made 5 minutes apart. It is not clear if the measurements were made at the same time each day.

The reader is referred to the March 2007 issue of *IHN* for a brief note on the benefit of chocolate in reducing the tendency for platelet clumping.

RESEARCH REPORT

Osteoporosis – Risk Factors, Prevention, and Treatment: Part I

by Hans R. Larsen, MSc ChE

Osteoporosis is characterized by a decrease in bone mass and density, causing bones to become fragile and increasing the risk of fractures. In the United States 26% of women 65 years or older, and more than 50% of women 85 years or older have osteoporosis. Over 1.5 million fractures, requiring about 500,000 hospitalizations and costing the health care system about 12 billion dollars, occur every year as a result of osteoporosis.[1] Men are not immune to osteoporosis, but the incidence is significantly lower than among women.[2] It is estimated that 1 in 3 women and 1 in 10 men now aged 55 years or older are destined to develop osteoporosis within their lifetime.[3]

Most commonly osteoporosis-related fractures occur at the wrist, spine, or hip. To better understand the risk factors for osteoporosis and to suggest ways of preventing and treating the disease, it is necessary to first gain a broad understanding of the process of bone formation.

Bones consist of a matrix of hydroxyapatite (calcium phosphate) and other minerals embedded in a cross-linked collagen matrix. The formation and maintenance of the bone structure is an ongoing, dynamic process. Up until the age of about 30 years the process involves mainly bone formation, but after this bone formation and bone resorption develop a delicate balance, which if bone resorption becomes dominant can lead to osteopenia (a forerunner of osteoporosis) and osteoporosis. There are two main types of cells involved in the process – osteoblasts, which promote the formation of new bone structure by increasing calcium content, and osteoclasts, which promote the resorption (demineralization of old bone) by releasing calcium into the blood circulation. Bone formation and resorption are also known as bone remodelling and take place continuously in the entire skeleton. The concentration of calcium in the blood is maintained within very narrow limits using the bone structure as a reservoir. The hormone calcitonin promotes the transfer of calcium into the bones, while parathyroid hormone (PTH) promotes the release of calcium from the bones.

Vitamin D is important in controlling PTH level with a deficiency leading to higher PTH concentration and subsequent demineralization. There is some evidence that an estrogen deficiency makes the osteoclasts more sensitive to PTH. Vitamin K is important in the synthesis of the gamma-carboxylated protein, osteocalcin. A deficiency of osteocalcin is associated with impaired bone formation (remineralization). Calcium, magnesium, boron, zinc, and strontium are all important constituents of the bone matrix with calcium being needed in the greatest amount.

Diagnosis

Osteoporosis and its “warning sign”, osteopenia, are diagnosed using a special x-ray technique called DEXA scanning (Dual Energy X-ray Absorptiometry). The scanning is painless and takes about 30 minutes. It measures the amount of minerals in the bones of the forearm, hip, and spine. The resulting number is called bone mineral density (BMD) and is used to determine if a patient has osteopenia or osteoporosis. The BMDs obtained for a particular patient are compared to average BMDs obtained in normal young adults of the same sex. Thus, if the patient’s BMD is within one standard deviation of the mean for young adults he/she is considered to have normal BMD. If the BMD is between 1 and 2.5 standard deviations below that of young adults, the patient would be classified as having osteopenia. If the patient’s BMD is more than 2.5 standard deviations below the young adult, then the diagnosis is osteoporosis. For most BMD tests, a decrease of one standard deviation below normal corresponds to a 10-12% decrease in bone density.

Although DEXA scanning provides useful information about bone mass, the results are not necessarily indicative of **bone strength**, which depends on both bone density and microscopic bone structure (rarely evaluated except in specific research projects).

Risk Factors and Prevention

Although the all-important risk factor of age cannot be changed at time of diagnosis, there are several risk factors, which can indeed be modified so as to reduce the risk of osteopenia and its progression to osteoporosis. Among the more important of these are:

- Lack of exercise
- Mineral and vitamin deficiencies
- Excessive protein intake
- Excessive coffee consumption
- Consumption of cola drinks
- Smoking
- Excessive salt intake

Certain medications (steroids such as prednisone, thyroid medications such as levothyroxine, antidepressants, and warfarin) have also been implicated as risk factors as have several diseases and disorders, notably celiac disease (sprue), elevated homocysteine levels, and hyperparathyroidism. There is also some evidence that a rapid heart rate is associated with osteoporosis in older women.[4]

Exercise
There is little doubt that physical inactivity leads to loss of bone mass – even in highly fit astronauts. There is also evidence that a structured program of load-bearing exercise such as regular walking can help prevent osteopenia and its progression to osteoporosis, especially if accompanied by supplementation with calcium and vitamin D.[5,6] Just recently Dr. Rittweger of the Institute for Biophysical and Clinical Research into Human Movement in the UK suggested that high strain rate exercises (weightlifting), while being beneficial in the prevention of osteopenia, may actually increase the risk of fractures in full-blown osteoporosis.[6] So, while high strain rate exercises may be appropriate for younger people, a more moderate program such as regular walking may be better suited to older people. In any case, the program to be effective needs to be accompanied by a proper diet, judicious supplementation, and avoidance of coffee, alcohol, smoking, and soft drinks (colas) which have all been proven to increase the risk of osteoporosis.[7]

There is some evidence that whole-body vibration exercise using a *Galileo* or *Power-Plate* machine can lessen osteoporosis-associated chronic back pain; however, there is no indication that it increases BMD when used in conjunction with alendronate.[8]

Vitamin D and Calcium
Several studies have shown that vitamin D deficiency is widespread. Researchers at Boston University School of Medicine found that 52% of postmenopausal women with osteoporosis had abnormally low vitamin D (25-hydroxyvitamin D) levels and commensurate high levels of PTH.[9] Vitamin D deficiency was more prevalent in women whose daily intake of dietary vitamin D was less than 400 IU. Swiss researchers recently reported that 64% of postmenopausal women with osteoporosis had a vitamin D deficiency and elevated PTH.[10]

The connection between vitamin D deficiency and osteoporosis was first reported by Meryl LeBoff and colleagues at Brigham and Women's Hospital in Boston. Their 1999 study found that 50% of women admitted with acute osteoporosis-related hip fracture were vitamin D deficient. They suggested that supplementation with vitamin D and accompanying suppression of PTH may reduce future fracture risk and help the healing of existing fractures. They concluded that vitamin D deficiency among the elderly is entirely preventable and recommended supplementation with calcium and 800 IU/day of vitamin D.[11]

Australian researchers have observed that vitamin D deficiency is also a major cause of osteoporosis and hip fractures among men. Their study involved 41 men (60 years and older) who were admitted with hip fractures. Known risk factors for osteoporosis and hip fracture were determined and compared to those of two control groups – one a group of 41 inpatients, the other a group of 41 outpatients all without hip fractures and aged 60 years or older. The researchers found that men in the hip fracture group had significantly lower blood levels of vitamin D (25-hydroxyvitamin D) than did men in the control group. Sixty-three per cent of the men in the hip

fracture group had a subclinical vitamin D deficiency (<50 nmol/L serum 25- hydroxyvitamin D) as compared to only 25 per cent in the control group. The researchers also noted that men with hip fractures and hospital in-patients had lower levels of calcium and testosterone than did the out-patient controls. About 89 per cent of the men with hip fractures and the in-patients were diagnosed with hypogonadism (low testosterone levels). The researchers conclude that a vitamin D deficiency is a major cause of hip fractures in elderly men.[12]

It is clear that vitamin D deficiency, irrespective of calcium status, is a critical risk factor for osteoporosis and associated bone fractures. Thus, it is fortunate that several clinical trials have concluded that vitamin D supplementation is effective in fracture prevention. Researchers at Harvard School of Public Health, after evaluating 14 reliable studies of oral vitamin D supplementation, concluded that daily supplementation with 700-800 IU of vitamin D reduced hip fracture risk by 26% and overall non-vertebral fracture rate by 23%. No benefit was observed with a daily dose of 400 IU (current RDA for women under the age of 70 years).[13]

A group of researchers at Harvard Medical School studied over 72,000 postmenopausal nurses for 18 years and found that those whose daily vitamin D intake exceeded 500 IU had a 37% lower risk of hip fracture than did women whose intake was less than 140 IU/day. They found no benefit of a high daily intake of milk or calcium on its own. The researchers point out that about 60% of the women in the survey had vitamin D intakes below those recommended by the Food and Nutrition Board (400 IU for women between the ages of 51 and 70 years and 600 IU for women older than 70 years). They also point out that the amount of vitamin-D produced by exposure to sunlight decreases significantly with age (due to thinning of the skin) and the use of sunscreens. They further suggest that the reason why milk showed no significant protective effect may be due to its content of vitamin A which recently has come under scrutiny in regard to its possible role as a negative factor in bone health. The researchers conclude that women should ensure an adequate daily intake of vitamin D either through the use of supplements or through increased consumption of fish such as salmon or sardines.[14]

The importance of daily supplementation with vitamin D is becoming increasingly clear. A team of American and Swiss researchers recently concluded that a daily intake of at least 1000 IU is required in order to achieve reasonable protection against the risk of osteoporosis, fractures, falls, and colon cancer. They suggest that an increase in the current RDA is warranted.[15] Dr. Reinhold Vieth and colleagues of the University of Toronto go even further. They found that 62% of supposedly healthy Canadians were deficient in vitamin D and that a daily intake of 4000 IU (100 micrograms/day) was needed to bring their level of 25(OH)D, the active metabolite of vitamin D, to the desirable level of 75 nmol/L. The researchers conclude that 4000 IU/day of vitamin D3 is a safe and desirable intake, but very specifically caution that their findings regarding vitamin D3 (cholecalciferol) cannot be applied to the synthetic version of vitamin D2 (ergocalciferol), the form most often used in North America. Vitamin D2 is far more toxic than vitamin D3 and produces unique metabolites not generated by D3. The researchers are very “down” on vitamin D2 and say, “It is an anachronism to regard vitamin D2 as a vitamin.”[16]

An adequate intake of calcium is clearly essential in achieving and maintaining sufficient bone mass due to the simple fact that calcium, in the form of hydroxyapatite, constitutes the major part of the bone structure. In combination with vitamin D it is effective in preventing bone loss and fractures. Ten years ago French researchers discovered that daily supplementation with 1200 mg of calcium and 800 IU of vitamin D3 (cholecalciferol) for 3 years reduced the number of hip fractures in a group of 3270 elderly women by 23%. The researches also noted that the bone density in calcium/vitamin D supplemented women increased by 2.7% over an 18-month period, while it decreased by 4.6% in the placebo group.[17] Since 1996 several other studies have verified the benefits of supplementation with calcium and vitamin D. In 1998 researchers at Johns Hopkins Medical School concluded that, “Optimal intakes of both calcium and vitamin D are relatively cost-effective, safe, and easily implemented approaches to maintain existing bone mass and assist in the prevention of fractures.”[18]

Dutch researchers report that 1000-1200 mg/day of calcium (elemental) plus 800 IU/day of vitamin D is effective in the prevention and treatment of osteoporosis.[19] German researchers, after evaluating several randomized, prospective, placebo-controlled clinical trials, conclude that supplementation with 800-1500 mg/day of calcium plus 400-1200 IU/day of vitamin D reduces the risk of falls and fall-related fractures in the elderly.[20] Indeed, the evidence that supplementation with calcium and vitamin D is beneficial in preventing and treating osteoporosis is incontrovertible.

It is, however, becoming increasing clear that a supposedly adequate calcium intake does not guarantee the absence of osteoporosis. The calcium must not only be ingested, it must also be absorbed and its excretion minimized. In other words, it is not the calcium intake per se that is important, but rather how much of it is actually retained in the body. Researchers at the University of Pittsburgh have found that the intake of fat and fiber significantly influences calcium absorption. Their study involved 142 healthy pre-menopausal white women who had enrolled in the Women's Healthy Lifestyle Project in 1995-96. The women had blood samples drawn three hours after consuming apple juice containing labeled (isotope) calcium. The blood samples were analyzed for calcium, 1,25 dihydroxyvitamin D (the active from of vitamin D), and PTH. The researchers found that about 35% (17-58%) of the labeled calcium had been absorbed. It was clear that women with a higher fat intake and a lower intake of fiber absorbed significantly more calcium than did women with less fat and more fiber in their diet. Women with high blood levels of vitamin D also showed increased absorption while women who consumed alcohol had decreased absorption. There is also some indication that a higher total calcium intake is associated with a lower rate of absorption. The researchers caution that it may only be certain types of fiber (eg. wheat bran) that inhibit calcium absorption. Fiber found in green leafy vegetables such as kale, broccoli, and bok choy may not be detrimental to absorption. They found no indication that genetic differences among the women were in any way related to calcium absorption. The researchers express the hope that their findings will encourage a second look at the current standard recommendation to emphasize a low-fat, high-fiber diet.[21]

The rate of excretion of calcium is also an important factor in determining its effectiveness in osteoporosis prevention. Dr. Christopher Nordin of Australia's Institute of Medical and Veterinary Science points out that is not the total calcium intake which determines bone strength (density), but rather the difference between what is taken in and what is excreted. Research has shown that for each gram of animal protein consumed one milligram of calcium is lost in the urine. This means that a 40-gram reduction in animal protein intake reduces the urinary calcium loss by 40 mg which, in turn, corresponds to a reduction in calcium requirements of 200 mg (assuming an absorption of 20%). A reduction in sodium (salt) intake of 2.3 grams also reduces urinary calcium loss by 40 mg lowering requirements by another 200 mg. So a person with a low intake of protein and salt might have half the calcium requirements of a person eating a typical North American diet. This and the fact that developing countries generally get more sunshine (vitamin D) than developed countries go a long way towards explaining the difference in the incidence of osteoporosis and bone fractures between different cultures and individuals. Dr. Nordin concludes that there is no single, universal calcium requirement, only a requirement linked to the intake of other nutrients especially animal protein and sodium.[22]

Dairy products like milk, cheese and yogurt are the richest sources of calcium followed by collards, spinach, beans, sardines and canned salmon. There is some indication that milk may not be an optimum source of calcium for older people. Researchers at the Boston University School of Medicine have studied the effectiveness of various sources of supplemental calcium in preventing bone loss in older women. Their study involved 60 postmenopausal women aged 65 years or older who did not suffer from osteoporosis and whose daily calcium intake from their regular diet was less than 800 mg/day. The women were randomly assigned to three groups. Group 1 supplemented with four 8-ounce glasses of vitamin D-fortified milk per day, group 2 took a 500 mg calcium carbonate supplement twice a day with meals, and group 3 took a placebo twice a day with meals. Bone density measurements of the spine (L2-L4) and thighbone (greater trochanter[GT]) were done at six-month intervals for a two-year period. After two years women in the placebo group (average daily calcium intake was 683 mg) had lost an average of 3% of their baseline bone mineral density in the trochanter area. This loss occurred exclusively during the winter months. Women in the milk group had an average daily calcium intake of 1028 mg and lost 1.5% of their bone density in the GT area. Women who supplemented with calcium carbonate tablets increased their daily intake to 1633 mg and suffered no bone loss in the GT area. The women in the supplement group also increased the bone density in their spine and femoral neck area by about 3%, while the placebo group women lost about 0.3%, and the milk group about 1.8%. The researchers conclude that 1000 mg/day of supplemental calcium is required in order to prevent bone loss in older women living in northern latitudes. They also point out that an adequate vitamin D intake (600-700 IU/day) is essential in order to prevent bone loss during the winter.[23]

Other researchers, however, have found that calcium is equally well absorbed from skim milk, calcium-fortified orange juice, and calcium carbonate tablets.[24] The most commonly used calcium supplements are calcium carbonate and calcium citrate. A comprehensive study comparing the bioavailability of calcium carbonate and calcium citrate found that calcium citrate was consistently better absorbed whether taken on an empty stomach

or with a meal.[25} Other research has shown that calcium carbonate is extremely poorly absorbed by people with low stomach acid even if taken with meals.[7] Inasmuch as low stomach acid (achlorhydria) is a common condition among older people, calcium citrate, calcium malate or calcium fumarate are all much better choices than calcium carbonate. Natural oyster shell calcium, dolomite, and bone-meal products should be avoided due to the potential for lead contamination and poor absorbability.[7]

As an added bonus, supplementation with vitamin D and calcium has also been found to reduce systolic blood pressure by about 10%.[26] Calcium citrate supplementation is also effective in reducing LDL cholesterol (the "bad" kind) and increase HDL cholesterol (the "good" kind").[27]

Calcium

The evidence that calcium supplementation on its own (without vitamin D) increases bone mass and helps prevent osteoporosis is somewhat sparser and more controversial. A 1998 study at the Boston University School of Medicine concluded that 2 x 500 mg of calcium carbonate taken with meals for two years improved bone density in the spine and femoral neck area by about 3%.[23] However, researchers at the Harvard Medical School found no benefit of calcium supplementation on its own.[7] It is quite likely that vitamin D status could explain the differences and also quite conceivable that an adequate vitamin D intake is actually more important than an increased calcium intake. However, as far as I know, no clinical trials have addressed this question.

In any case, there would seem to be little advantage in consuming more than the RDA (1200 mg/day) of calcium and a great advantage in ensuring that this intake is accompanied by a vitamin D3 intake of at least 1000 IU/day. Low-fat dairy products contain as much calcium per serving as do high-fat products. Calcium supplements should be taken in divided doses of 500 mg or less and preferably between meals except for calcium carbonate, which must be taken with meals because of its poor absorption. Calcium citrate is the preferred supplement for older people or individuals with inadequate stomach acid production. A daily calcium intake of up to 2000 mg appears to be safe for most individuals.[28] Antacid medications containing aluminum significantly increase the loss of calcium through the urine, as does a diet high in animal protein and salt.

It is commonly believed that a high calcium intake increases the risk of forming kidney stones. Researchers at the Universities of Michigan and Arkansas, however, provide convincing proof that this contention is wrong and that a high dietary intake of calcium actually reduces the risk of stone formation. Their study involved 1309 women aged between 20 and 92 years. The women's intake of calcium, oxalate-containing foods, and ascorbic acid was estimated using the National Cancer Institute Food Frequency Questionnaire. The women resided in three different communities where the calcium content of the water supply varied between 15 mg/mL and 375 mg/mL. Analysis of the collected data showed that women with medically diagnosed kidney stones (44 out of 1309 or 3.4 per cent) had an average intake of 843 mg/day of calcium from food, supplements, and water while women without a history of kidney stones had an average intake of 1070 mg/day. The main difference in calcium intake was associated with food intake rather than with water or supplement intake. There was no significant difference in total fluid intake or intake of oxalate-rich foods between women who had kidney stones and those who had not. Neither was there any association between the intake of ascorbic acid (vitamin-C) and the risk of kidney stones. Bone mineral density and incidence of fractures were no different between women with or without kidney stones when the data was adjusted for age, body mass index, and calcium, oxalate and ascorbic acid intake. The researchers speculate that a high calcium diet may be protective because the calcium binds to the oxalate in the intestines and thereby prevents it from reaching the kidneys. They conclude that increasing the intake of dietary calcium may be protective against kidney stones and that an increased dietary calcium intake is not associated with a greater risk of forming renal stones.[29]

Italian researchers have confirmed that a normal calcium intake does not increase the risk of kidney stones in men. Their randomized clinical trial included 120 men with a history of kidney stones (idiopathic hypercalciuria). Sixty of the men were assigned to a low-calcium diet (avoidance of milk, yogurt and cheese) while the other sixty were assigned to a normal calcium diet that was low in animal protein (52 grams/day max.) and salt.

After five years 23 of the men in the low-calcium diet group had experienced a recurrence of kidney stones as compared to only 12 men in the normal calcium diet group. Thus the men in the low-calcium group had twice the risk of recurrence than did the men in the normal calcium, low protein and low salt group. Says Dr. David

Bushinsky of the University of Rochester, "Physicians should no longer prescribe a low-calcium diet to prevent recurrent nephrolithiasis in patients with idiopathic hypercalciuria".[30,31]

Researchers at the Pitie-Salpetriere Medical School found that ingestion of as little as 0.5 liters (18 oz) of calcium-rich mineral water (*Vittel)* has an immediate and profound effect on the prevention of bone loss. Their experiment involved 12 healthy young men who participated in a series of tests designed to compare the effects of a natural mineral water containing 345 mg/L of elemental calcium with that of a mineral water containing only 10 mg/L. The study participants (after an overnight fast) drank 0.5 liters of either of the two mineral waters and then had blood and urine samples collected for the next four hours. The ingestion of the calcium- rich water significantly inhibited the secretion of parathyroid hormone after one hour and the effect was still evident after four hours. The blood level of type 1 collagen cross-linked C- telopeptide (CTx) also declined markedly after drinking the calcium-rich water. Low levels of parathyroid hormone and CTx are both beneficial in that they are associated with a reduction in bone loss (resorption). The researchers conclude that drinking calcium-rich mineral water throughout the day will not only ensure an adequate water intake, but will also help to preserve bone mass.[32]

Magnesium

Magnesium is an extremely important mineral and is involved in the functioning of more than 200 enzymes as well as being a key player in the body's energy (ATP) cycle. About half of the body's magnesium stores can be found in bones, so it is clearly also a very important mineral as far as osteoporosis prevention is concerned. Unfortunately, magnesium deficiency (plasma/serum level below 0.76 mmol/L) is very common ranging between 15% and 50% of the population.[33-36] Average dietary intakes of magnesium are also generally well below recommended intakes.[37] A recent study found that 74% of a cohort of 2000 elderly men and women did not consume the recommended 400 mg/day. This same study also concluded that a high magnesium intake is associated with a significantly higher bone density in older white men and women. Every 100 mg/day extra intake of magnesium was found to correspond to a 2% increase in whole-body bone mass. This compares to an approximate 2% increase per 400-mg/day increase in calcium consumption. It is thought that magnesium may act as a buffer for the acid produced by the typical Western diet and may also replace calcium in the hydroxyapatite part of bone, thus resulting in a stronger structure.[38] There is also evidence that magnesium suppresses bone resorption (demineralization) at least in younger people.[39]

A clinical trial in Israel showed that postmenopausal women suffering from osteoporosis could stop further bone loss by supplementing with 250-750 mg/day of magnesium for two years. Some (8%) of the treated women even experienced a significant increase in trabecular bone density. Untreated controls lost bone mass at the rate of 1% a year. Another experiment in Czechoslovakia found that 65% of women who supplemented with 1500 to 3000 mg of magnesium lactate daily for two years completely got rid of the pain and stopped further development of deformities of the vertebrae. Other studies have shown that magnesium is helpful in the treatment of cardiac arrhythmias and that an adequate intake helps prevent atherosclerosis.[40]

Legumes, tofu, seeds, nuts, whole grains, and green leafy vegetables are good sources of magnesium. Magnesium glycinate (chelated magnesium) is the most bioavailable and best tolerated supplement. Magnesium citrate is also highly available, but may cause loose stools. The common form of magnesium used in supplements, magnesium oxide, is essentially useless in that only about 4% of the ingested amount is actually absorbed.[41]

Strontium

A major study published in the *New England Journal of Medicine* in 2004 concluded that supplementing with 2 grams/day of oral strontium ranelate (*Protelos*) reduced the risk of vertebral fractures by 50% in a group of 1649 postmenopausal women with low BMD.[42] This landmark study sparked a flurry of interest in the use of strontium compounds for the prevention and treatment of osteoporosis. Additional studies have shown that strontium is well tolerated in adults and highly effective in increasing bone formation and decreasing bone resorption.

In a recent trial involving 5091 postmenopausal women with osteoporosis, hip fracture was reduced by 36% and vertebral fracture by 39%. This trial also clearly demonstrated the beneficial effect of strontium on BMD. Increases of 8.2% at the femoral neck and 9.8% at total hip were observed in women treated for 3 years.[43] A

recent Cochrane review concluded that strontium ranelate is effective in both prevention and treatment of osteoporosis. Doses used in the trials ranged from 125 – 1000 mg/day for prevention to 500 – 2000 mg/day for treatment of existing osteoporosis. A 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures were demonstrated over a 2-year period with 2 grams/day of strontium ranelate (containing 700 mg of elemental strontium).[44]

It is not clear why strontium has such a beneficial effect on bone health, but it has recently been reported that commercial foods grown on fields using synthetic fertilizers, pesticides, and herbicides have appreciably lower levels of strontium than their organic food counterparts.[3] Although recent studies have focused on the use of strontium ranelate, previous studies have found the following forms of organically-bound strontium to be equally effective – strontium gluconate, strontium carbonate, strontium lactate, and strontium chloride.[3]

Strontium ranelate was developed in France and unfortunately, is not available in North America.

Zinc

A low dietary intake of zinc and accompanying low blood levels has been associated with an increased risk of osteoporosis in women. Researchers at the University of California have found that an adequate zinc intake is equally important for men. Their study involved 396 men aged between 45 and 92 years who had their bone mineral density (BMD) measured at baseline (in 1988-1992) and 4 years later. Plasma zinc level correlated well with the total intake from diet and supplements. The average daily intake was 11.2 mg and the mean plasma zinc concentration was 12.7 micromol/L. The researchers observed that men with a low zinc intake and plasma concentration were significantly more likely to have osteoporosis of the hip and spine.[45]

Boron

Boron is also a very important mineral in osteoporosis prevention. Researchers at the U.S. Department of Agriculture found that women who supplemented with 3 mg of boron daily reduced the amount of calcium excreted in their urine by 44%. The conclusion of the study was that boron improves the metabolism of calcium and magnesium.[46]

Potassium

A high salt diet has been found to significantly increase urinary calcium excretion and bone loss. Supplementing with 90 mmol/day of potassium citrate (3500 mg of elemental potassium) will prevent this detrimental effect.[47] Researchers at the University of California believe that bone loss is partly due to a lifelong leaching of calcium from the skeleton brought about by the body's constant need to neutralize the internal acidity generated from the daily diet. The researchers also believe that daily supplementation with potassium bicarbonate can prevent further bone loss and even promote bone formation. Their recent experiment involved 18 postmenopausal women aged 51 to 77 years. The women were put on a controlled diet which contained the following approximate amounts of nutrients per 60 kg of body weight: calcium – 652 mg, phosphorus – 871 mg, potassium – 59 mmol (2300 mg), sodium – 119 mmol, protein – 96 grams, and energy – 1995 kcal. After 22 days on the diet and a 6-day control period, the women were given an alkali supplement for 18 days. The supplement consisted of an aqueous solution of 60-120 mmol/day of potassium bicarbonate (2300-4700 mg of elemental potassium) per 60 kg of body weight. Although the amount of calcium excreted (through stools and urine) was consistently greater than the daily intake, the shortfall was significantly less during the period of potassium bicarbonate supplementation. The researchers conclude that supplementing the diet with potassium bicarbonate helps maintain and perhaps even increase bone mass because the potassium bicarbonate, rather than calcium leached from the bones, is used to neutralize the excess acid produced by a normal diet.[48,49]

Vitamin A

Vitamin A (retinol) is important for vision and a deficiency has been associated with poor night vision. Vitamin A is also essential for proper immune function and is intimately involved in the synthesis of glycoproteins. The recommended daily allowance (RDA) is 700 micrograms/day (3500 IU) for women and 900 micrograms/day (4500 IU) for men. The official upper safe limit for daily vitamin A intake is set at 3000 micrograms/day (15,000 IU), but some recent evidence suggests that this may be too high.

It is a well-established fact that the incidence of hip fractures is exceptionally high in Sweden and Norway. Researchers at the Uppsala University in Sweden believe that an excessive intake of vitamin A may be involved.

Vitamin-A intake is traditionally higher in the Nordic countries where cod liver oil is commonly taken as a supplement and margarine and milk are often fortified with both vitamins A and D. The researchers studied a group of 175 women (aged 28 to 74 years) and found that their bone density (measured in the spine and thigh bone) correlated with their vitamin A intake. Women with an average daily intake of more than 7500 IU (1.5 mg) were found to have a 10 per cent lower bone mineral density in the thighbone (femoral neck) and a 14 per cent lower density in the lumbar spine. This relationship held true even after correcting for numerous other factors related to bone density such as smoking, physical activity level, menopausal status, calcium and vitamin D intake, etc. The researchers also evaluated the correlation between vitamin A intake and hip fracture in a group of 247 women with hip fracture and 873 age-matched controls (40 to 76 years of age). They found that the risk of hip fracture was twice as high among women who consumed more than 7500 IU/day as among women consuming 2500 IU/day (0.5 mg) or less. They point out that animal studies have shown that excessive vitamin A intakes are correlated with accelerated bone resorption and spontaneous fractures and conclude that an excessive dietary intake of vitamin A is associated with osteoporosis in humans.[50]

Vitamin B12

Vitamin B12 (cobalamin) is an important water-soluble vitamin. In contrast to other water-soluble vitamins, it is not excreted quickly in the urine, but rather accumulates and is stored in the liver, kidney, and other body tissues. As a result, a vitamin B12 deficiency may not manifest itself until after 5 or 6 years of a diet supplying inadequate amounts.

Blood serum level of vitamin B12 is difficult to measure accurately, so instead of measuring cobalamin level, many studies measure the level of methylmalonic acid (MMA). MMA is a precursor to metabolic reactions controlled by cobalamin, so if its level is abnormally high, then the level of cobalamin is abnormally low. The normal blood level of vitamin B12 ranges between 200 and 600 picogram/mL (148-443 picomol/L). A MMA level greater than 271 nmol/L indicates a vitamin B12 deficiency. The classical vitamin B12 deficiency disease is pernicious anemia, a serious disease characterized by large, immature red blood cells.

Vitamin B12 is important in DNA synthesis and may affect bone formation. It has been linked to osteoblastic activity in clinical studies and cell culture.[51] A 1992 study involving a group of postmenopausal women in Rochester, Minnesota reported an almost 2-fold increase in the risk of hip and spine fractures, and an almost 3-fold increase in wrist fractures among women with pernicious anemia when compared to normal controls.[52] More recently, researchers at the University of California (SF) found that women with low serum vitamin B12 levels (below 280 pg/mL) lost bone mass in the hip more rapidly than did women with B12 levels above 280 pg/mL (1.6% loss/year vs. 0.2% loss/year).[53]

The Framingham Offspring Osteoporosis Study (1996-2001) examined the relationship between plasma vitamin B12 status and BMD in 2576 adults. The conclusion was that men with low plasma vitamin B12 levels had significant lower BMD at the hip, while women with low levels had significantly lower BMD at the spine. The Framingham researchers conclude that low vitamin B12 status may be a risk factor for low BMD.[54]

The association between low vitamin B12 status and inferior BMD is not limited to the older generation. A Dutch study observed that vitamin B12 levels were significantly lower and MMA levels significantly higher in adolescents with low BMD.[55]

The amount of vitamin B12 actually needed by the body is very small, probably only about 2 micrograms or 2 millionth of a gram/day. Unfortunately, vitamin B12 is not absorbed very well so much larger amounts need to be supplied through the diet or supplementation. The richest dietary sources of vitamin B12 are liver, especially lamb's liver, and kidneys. Eggs, cheese and some species of fish also supply small amounts, but vegetables and fruits are very poor sources. Several surveys have shown that most strict, long-term vegetarians are vitamin B12 deficient. Many elderly people are also deficient because their production of the intrinsic factor needed to absorb the vitamin from the small intestine decline rapidly with age.

Fortunately, oral supplementation with vitamin B12 is safe, efficient and inexpensive. Most multi-vitamin pills contain 100-200 microgram of the cyanocobalamin form of B-12. This must be converted to methylcobalamin or adenosylcobalamin before it can be used by the body. The actual absorption of B12 is also a problem with supplements. Swallowing 500 micrograms of cyanocobalamin can result in absorption of as little as 1.8

microgram so most multivitamins do not provide an adequate daily intake. The best approach is to dissolve a sublingual tablet of methylcobalamin (1000 micrograms) under the tongue every day. That will be sufficient to maintain adequate body stores. However, if a deficiency is actually present then 2000 microgram/day for one month is recommended followed by 1000 microgram/day. Some physicians still maintain that monthly injections of vitamin B12 is required to maintain adequate levels in the elderly and in patients with a diagnosed deficiency. There is however, no scientific evidence supporting the notion that injections are more effective than sublingual supplementation.

Lycopene

The carotenoid lycopene is a powerful antioxidant, particularly abundant in tomatoes. University of Toronto researchers have discovered that lycopene has profound effects on bone turnover. It inhibits the formation of osteoclasts (the cells that promote demineralization of bone) and promotes the formation of osteoblasts (the cells that put calcium back into the bone)[56,57] In a recent study involving 33 postmenopausal women researchers concluded that study participants with a high dietary intake of lycopene exhibited less protein oxidation and production of cross-linked N-telopeptides of type I collagen. The researchers conclude that lycopene may be beneficial in reducing the risk of osteoporosis.[58] Lycopene can be obtained from tomatoes or, even better, from processed tomato products such as tomato paste and juice. Supplements are also effective in increasing blood levels of lycopene.[59]

Vitamin C

Epidemiological studies have shown that vitamin C exerts a positive influence on bone formation.[60] A 2001 study examined the effect of vitamin C supplementation on bone mineral density (BMD) in a group of 994 postmenopausal women. In this group, 277 were regular users of vitamin C with an average daily intake of 745 mg (range of 100 – 5000 mg/day). The average duration of use was 12.4 years and 85% had supplemented for more than 3 years. Women who took vitamin C were found to have a significantly high BMD in the hip and forearm than women who did not. The difference was particularly impressive in women supplementing with more than 1000 mg/day.[61] Australian researchers recently reported that supplementation with vitamin C or E may enhance the formation of osteoblasts while retarding the formation of osteoclasts; although they did not observe an increase in BMD as such in the 533 women who participated in the experiment, they conclude that, “antioxidants may play a role in preventing osteoporosis.”[62]

Vitamin K

Vitamin K comes in two forms – phylloquinone (vitamin K1) and menaquinone (vitamin K2). Phylloquinone is found in dark green vegetables like spinach, broccoli and kale. Green, but not black tea is also a rich source of phylloquinone. Menaquinone is found in meats, butter, cheese and fermented foods (especially natto) and can also be produced by conversion of vitamin K1 in the intestinal tract. This conversion, however, is compromised after a course of antibiotics. The RDA for total vitamin K intake is 90 micrograms/day for women and 120 micrograms/day for men, and is essentially the amount required for the synthesis of coagulation factors in the liver. The RDA does not consider that vitamin K (especially K2) is also required outside of the liver (extrahepatic), particularly to ensure healthy bones and blood vessels.[63] Several studies have shown that about 50% of the general population have daily vitamin K intakes below the RDA.[64]

The main role of vitamin K is to act as a cofactor for the conversion of glutamate into gamma-carboxyglutamate, which, in turn, is involved in the synthesis of osteocalcin, the hormone that promotes bone formation. Several epidemiological studies have concluded that a vitamin K deficiency causes reductions in bone mineral density and increased the risk of fractures.[65]

Other studies have shown that a high intake of vitamin K is associated with a substantially reduced risk of hip fracture and that a daily intake below 109 micrograms/day is associated with an increased risk.[66,67] Several studies have also concluded that supplementation with a combination of vitamin K1, vitamin D3, and calcium is highly effective in increasing BMD.[68,69] Dutch researchers treated 188 postmenopausal women for 3 years with supplements (calcium, magnesium, zinc, vitamin D3, and vitamin K1) and found that the annual rate of bone loss decreased by 35 to 40%.[70]

It is likely that between 200 and 500 micrograms/day of dietary vitamin K may be required for optimal gamma-carboxylation of osteocalcin.[64] Unfortunately, relatively few people achieve such high intakes from their diet.

Thus, it is fortunate that available evidence regarding relative bioavailabilities suggests that 100 micrograms/day of vitamin K in the form of supplements is equivalent to 200 – 500 micrograms/day obtained from the diet.[64] Vitamin K has a very wide safety range. No adverse effects or hazards have ever been associated with supplementation with natural vitamin K.[71]

To be continued in October issue – Part II: Diet and Lifestyle, Associated Diseases and Disorders, Alternative and Conventional Treatment

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 6 **September 2007** **1st Year**

I recently noticed a newsletter author commenting that woman's health seemed to receive much more attention than men's health. He was obviously referring to gender specific problems which would include female cancers and prostate problems. While it is indeed true that such publications as the New England Journal of Medicine's popular newsletter Journal Watch has a women's health section and as well a breast cancer section, it lacks the equivalent for men and that includes the absence of sections devoted to prostate problems, prostate cancer or even male urology. It is nevertheless important to realize that the twin subjects of prostate cancer and prostate enlargement have an associated literature and research base which is both very large and highly significant. The present state of knowledge in these two areas is extensive, sophisticated, and offers significant clinical guidance to those who treat these conditions. Men's health, and in particular these two topics, have definitely not been neglected, and in fact, aspects from diagnosis to treatment have been very thoroughly and comprehensively researched from the laboratory to the bedside. The treatment of both prostate enlargement and prostate cancer involves a number of very well researched options and the information base is growing by the month. Leaders in the field have spent most of their careers in research and clinical practice restricted to the prostate.

Men and indeed their spouses and partners, need to realize the importance of the prostate as a determinant of a man's quality of life, and this importance extends far beyond its purely sexual aspects since when problems arise, the associated risks range from severe urinary problems to death. Primary prevention, early diagnosis, unnecessary treatment and the balance between treatment risks and benefits become huge issues in connection with both quality of life and having a normal life expectancy. While it is often said that most men die with prostate cancer rather than from it, it is probably also true that it is much better to die from something other than this form of cancer. It is important issues such as these that are addressed in our book "The Prostate and Its Problems". Unfortunately, there is a natural built-in denial syndrome strongly connected with the prostate which inhibits men from admitting the presence of problems or seeking knowledge which could be very beneficial in connection with this critical aspect of their lives.

In this issue we discuss recent research related to prostate enlargement, also known as benign prostatic hyperplasia (BPH). Emphasis is on drug treatment options which will most certainly be suggested when natural remedies become ineffective or when ignoring the warning signs no longer works. Many readers have an understandable aversion to taking pharmaceutical drugs, but for advanced BPH there do not seem to be other first-line non-invasive treatment options that promise a good probability of benefit. Obviously, men in their 40s and 50s should become knowledgeable in the area of primary prevention and maximum inhibition of early progression in order to avoid being in the position of needing these so-called patent medicines for as long as possible, if not forever.

The second featured subject involves prognosis after recurrence. Recurrence, i.e. the "return" of the cancer after definitive treatment, is much more common than may be realized, partly because of the uncertainty in the stage of development of the cancer at the time of diagnosis which results is treating some who already have

cancer which can not be "cured" by radiation or surgery because is has already started to spread. Once recurrence has taken place, there are options, and what to do depends critically on the clinical judgment call termed the prognosis. Two papers are discussed which relate to this matter.

Wishing you continuing good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at http://www.yourhealthbase.com/prostate/book.htm

NEW RESULTS REGARDING PROSTATE ENLARGEMENT

The progressive enlargement of the prostate, also called benign prostatic hyperplasia or BPH, which occurs as a man ages, can become a major determinant of his quality of life and a significant aspect of its deterioration. Progression can be slow and easily ignored until acute symptoms demand attention. Many men are unaware that there are natural remedies which have been demonstrated to equal pharmaceutical intervention in the early stages of this disorder. See Chapter 2 of our book where natural prevention is discussed at length.

There are two distinct classes of drugs used to treat BPH, the so-called alpha-blockers and the 5-alpha reductase inhibitors (5ARI). The former works mainly through the nervous system whereas the second acts to reduce the production of dihydrotestosterone, a hormone linked to benign prostate growth. Initial drug treatment generally involves so-called alpha-blockers which historically were used for blood pressure regulation but have become the first line treatment for BPH. The choice of an alpha-blocker as the initial response resides mainly in its rapid action to reduce urinary symptoms associated with prostate enlargement. Older alpha-blockers require so-called titration to build up the desired dose since otherwise they may produce undesirable blood pressure changes. Newer alpha-blockers do not have this problem since they are what is termed *uro-specific* and do not significantly influence blood pressure.

There are only two 5ARIs approved for the treatment of BPH, finasteride (Proscar) and dutasteride (Avodart). The former inhibits one form of the enzyme 5ARI whereas the latter inhibits the action of both forms. Low doses of Proscar are also used to treat male-pattern baldness (Propecia, 1mg doses of finasteride). Both in even minute quantities can produce very serious birth defects if absorbed or ingested by pregnant women and women in general should avoid all contact with the pills. Both 5ARIs take several months to produce significant urinary symptom reduction, and it is for this reason that the alpha-blocker is generally used first. However, the 5ARIs also have different side effects as compared to the alpha-blocker. An approach to treating BPH which is growing in popularity is called *combined therapy* and involves using both an alpha-blocker and a 5ARI. The reason is simply that the alpha-blocker does not reduce the prostate volume nor does it significantly reduce the risk of progression of BPH and especially progression to an acute urinary retention episode (translation, one can't pee at all!) or surgery to relieve a serious urinary obstruction, whereas the 5ARIs are effective in this regard.

Several recent studies are of interest. The first was part of the now famous Prostate Cancer Prevention Trial (PCPT) which found that treatment with Proscar reduced the incidence of low-grade or localized prostate cancer but slightly increased the risk of finding high-grade tumors. Incidentally, this latter observation has still to be accepted as valid and not due to residual confounding. In the study in question, Proscar was found to improve the sensitivity of the digital rectal examination for detecting prostate cancer (1). The presence of prostate cancer was determined by biopsy and it was found that the DRE was significantly more sensitive in detecting cancer in men receiving Proscar as compared to a placebo, and was also more sensitive in detecting high-grade (Gleason 7 or 8-10) cancers (see our book for a discussion of the Gleason Score). It is of interest that the PCPT trial also found that taking Proscar also significantly increased the sensitivity of the PSA test. The authors point out that given these two results, it is remarkable that they found a 24.8% decrease in cancer detected by biopsy since the Proscar improved cancer detection with both the DRE and PSA test and thus the magnitude of the cancer

reduction associated with Proscar therapy may in fact have been greater than observed. While in the PCPT the mean prostate volume reduction was about 24%, the role of this reduction on the above observations is not clear. However, even with this improvement of the performance of the DRE, a suspicious DRE still produces a large number of negative biopsy results, especially for men with low PSA.

In a study related to the PCPT, a Finish group looked at the prostate cancer risk among users of either Proscar or an alpha-blocker (2). In both cases, an increase of incidence was observed, with those on Proscar having a lower risk than those taking an alpha-blocker. This study was based on Finish government registries of prescriptions and cancer diagnosis. The authors conclude that these results merely indicate that there was a higher level of diagnosis for men with BPH due to greater medical attention. In fact, the authors point out that almost 90% of men over 50 years of age have lower urinary tract symptoms but only about 16% are actually treated for BPH. In addition, the lower incidence observed for Proscar treated individuals is consistent with the results from the PCPT. Presumably the risks (false positives, over diagnosis, over treatment) associated with seeking medical attention in this context are outweighed by the benefits of early or timely diagnosis and treatment, although those who worry about unnecessary treatment of indolent cancer might disagree.

The two 5ARIs are of course in head-to-head competition in the marketplace with Avodart currently receiving aggressive TV advertising in the US and by default also in Canada. Avodart, is not really a me-too product since it is a dual enzyme inhibitor, but in comparative studies both produced similar long-term results (see our book for details including side effects). In a recent study based on an integrated medical and pharmaceutical data base in the U.S. the following question was addressed: in men on combined therapy, is there any difference in when the alpha-blocker is withdrawn in favor of continuing just monotherapy with a 5ARI? It was found that users of Avodart discontinued their alpha-blocker significantly earlier than the Proscar users, suggesting that the dual acting Avodart provided symptomatic relief earlier than Proscar. The authors point out that this could reduce costs somewhat while maintaining adequate symptom control (3). Such savings may be of more interest to managed care organizations than to the individual.

The one strong motivation for choosing either combination therapy or monotherapy with a 5ARI is the reduction in risk of acute urinary retention and especially the risk of subsequent prostate surgery or some other less invasive procedure, either of which is accompanied by significant morbidity. Thus the head-to-head comparison of Proscar and Avodart in this context assumes particular interest. A study has just been reported which constitutes the first direct comparison of therapeutic outcomes for these two drugs. It was found that after 5 months of 5ARI treatment, the rate of acute urinary retention during the subsequent 7 months was 5.3% in the Avodart group and 8.3% in the Proscar group. After controlling for confounding, the Avodart group was 49.1% less likely to experience an acute urinary retention episode than the patients treated with Proscar. Also, 1.4% of Avodart patients as compared to 3.4% of Proscar patients required prostate surgery for urinary obstruction. (4).

While many readers of this newsletter probably have a natural and well justified aversion to pharmaceutical intervention, an attitude shared by your editor, the urinary tract problems caused by prostate enlargement in some cases can not be indefinitely controlled by natural therapies such as Saw Palmetto and other products described in our book. Also, as discussed in the book, the success of these natural approaches in treating the initial stages of BPH are very good indeed, something that mainstream medicine does not acknowledge and simply refers to studies where natural remedies have failed without taking into account that the trials were on individuals with advanced BPH. However, when the point is reached where the natural therapy stops working, it is not clear that there are alternatives other than drugs or in the worst case scenario, surgery or some other approach equally frightening (e.g. cooking or freezing the prostate). Also, since the 5ARIs consistently produce significant reductions in prostate volume and concomitant reductions in urinary problems and a delay of progression to acute urinary retention, they seem by default to be the next step after the more innocuous alpha-blockers fail to control symptoms and are attractive for combined therapy. There are of course side effects, but if one has reached the point where urination has become extremely difficult, painful, frequent, etc., side effects take on a somewhat different perspective than when considered in a more abstract setting.

From what has been presented above, it is obviously of interest to review the so-called modifiable risk factors for BPH, since this is an important initial step in primary prevention. J. K. Parsons from the University of California San Diego Medical School has just published a review that addresses this issue (5). His review of the literature does not turn up much. Obesity and diabetes increase the risk of BPH whereas physical activity and moderate

alcohol consumption decrease the risk. For alcohol, 30-60 grams per day compared to either abstinence or 5 grams per day yielded a risk reduction of about 40% (one drink typically contains about 12-15 grams of alcohol) whereas walking 2 hours/week or more vs. no exercise gave a risk reduction of about 27%. Diabetes, high fasting blood glucose, hypertension, large waist circumference and obesity all produced increased risks that ranged from 30% to 250%. Some of these are components of the Metabolic Syndrome, a cluster of adverse indications for so many health problems that avoiding the Metabolic Syndrome should receive a very high priority in anyone's program for staying healthy, quite apart from the relationship to prostate problems.

PROSTATE CANCER TREATMENT AND PROGNOSIS

One task facing physicians treating prostate cancer is achieving a reliable prognosis after treatment based on the best available evidence. When the treatment involves surgery, the pathological examination of the removed prostate and associated tissues provides valuable information which is obviously unavailable when radiation therapy is employed as primary therapy. As discussed in our book, there are online calculators and nomograms available which allow patients and doctors to calculate probabilities of recurrence but prostate cancer-specific mortality is also an issue, especially if a decision is required as to eligibility for entry into an experimental drug program since such studies are generally restricted only to the highest risk patients. This matter has been studied by D'Amico *et al* where they estimated prostate cancer specific mortality after surgery or radiation therapy in men with one or more high-risk factors. These factors were a PSA velocity of > 2 ng/mL per year during the year before diagnosis (biopsy), a biopsy Gleason score of ≥7 or a PSA level ≥ 10 ng/mL or a clinical T2b or higher disease (tumor palpable at DRE or evidence of invasion of surrounding tissue). Men with a PSA velocity > 2 ng/mL per year had a significantly higher risk of dying from prostate cancer compared with men having any other single high-risk factor. The authors conclude that these men should be considered for randomized trials evaluating the impact of what they term systemic agents (e.g. chemotherapy) on the normal standard of care for these individuals at high risk (6).

In a related study, Freedland *et al* examined predicative factors for mortality after radical prostatectomy for prostate cancer. The study followed 379 men who had PSA recurrence (increasing PSA) after surgery for a mean of about 11 years. The prognostic factor used was PSA doubling time (PSADT) which is of course closely related to PSA velocity. Among patients with post-surgical PSADT of less than 15 months, prostate cancer accounted for 90% of the deaths. Only patients in the slowest PSADT subgroup (≥ 15 months had a greater risk of death from competing causes as compared to death from prostate cancer. The mean age at surgery was about 60 years (7).

These two studies solidify the role of PSADT or PSA velocity in the assessment of the probability of post treatment mortality due to prostate cancer. Men with very short doubling times may want to seek out experimental drug programs and as well, examine alternative approaches such as are described in our book. Attention is also directed to previous issues of the Prostate Monitor where the use of pomegranate juice to delay or arrest PSA progression due to post-treatment recurrence is discussed.

Recurrent prostate cancer after surgery to remove the prostate occurs in approximately 25% of patients. This reflects the fact that not all patients receiving surgical therapy for prostate cancer are ideal candidates but nevertheless the surgical option appeared to offer more potential reward than risk. Recurrence is frequently treated by radiation, generally termed salvage radiation therapy (SRT). An area somewhat larger than that occupied by the prostate is irradiated in the hope of killing any cancerous tissue or cancer cells that remained after surgery, i.e. locally recurrent cancer. Obviously if the cancer has spread, this approach is doomed to ultimate failure and ultimately death from prostate cancer unless a fatal comorbidity intervenes. The first sign of recurrence is generally an increasing PSA, but the problem faced by clinicians is differentiating between local recurrence that would benefit from SRT and systemic recurrence which would not. In a recent study, Stephenson *et al* have attempted to develop a predictive tool that would provide 6 year post-surgical progression free probabilities (8). Eleven parameters available after surgery were used to construct a so-called nomogram, which is a graphical device which allows the weighting of each factor to come up with a total number of points which then is used for the prediction of progression-free survival. Men experiencing recurrence under the circumstances described above should ask their physician about this nomogram and perhaps suggest that it be

used to give an indication of the seriousness of their problem. Incidentally, the authors point out that nearly half of the patients with recurrence after surgery have long-term favorable PSA response to SRT when treatment is administered at the earliest sign of recurrence. This in fact points to one of the advantages of the radical prostatectomy over primary radiation therapy—the prostate is gone, and thus recurrence can be picked up very early, whereas with primary radiation therapy the prostate remains in place, PSA drops slowly, levels off and then can provide information about recurrence if a significant rise takes place. There also can be a false alarm called the PSA bounce which can be very upsetting to the patient but in fact not clinically significant. In general, what constitutes a significant rise is debatable and overall, there is generally a considerable delay between treatment and the conclusion that genuine recurrence is present. In addition, the options after the failure of primary radiation therapy are quite different since surgery at this point is generally much more difficult. See our book for a detailed discussion of this matter. There are important issues, and in many cases the patient is given a choice between two or more primary modes of treatment, or even doing nothing, and needs knowledge upon which to base an intelligent decision.

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