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William R. Ware, PhD - Editor

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This issue features vitamin D. Your editor apologizes if readers have tired of the constant stream of reports on the benefits of this vitamin, but the recent results seem too interesting to simply file away.

We start with political matters. One, the call by the World Health Organization for randomized clinical trials of vitamin D, has to do with the almost religious belief that the only therapies that merit a second glance are so-called evidence based and must be backed by randomized, placebo controlled, double blind intervention studies. One can sympathize with the believers since they and everybody else have been confused a number of times with results from observational studies that failed to be confirmed in randomized clinical trials. Some of these failures of the two research approaches are not real but simply reflect complex issues. Also, not all randomized clinical trials are properly carried out or even properly designed. Examples include doses which are meaningless and the placebo groups allowed to take the intervention substance or substances ad libitum. The benefits of vitamin D are implicated in many disorders. Randomized intervention trials involving apparently healthy individuals of all ages would have to be unrealistically large to produce statistically significant results, and should be long term. The incidence rates of specific disorders available for stratification would be too low unless huge numbers were enrolled. Thus the cost would be prohibitive and would only be paid by governments or charitable organizations since vitamin D is not a patent drug. Recommended intakes of vitamin D and safe limits are also now under consideration by a committee and the end result will no doubt be a consensus report. Yet very large doses appear safe and the arguments in favour of this view are compelling, given the huge pharmacologic doses administered and the large amounts generated by sun exposure. Nevertheless, it is quite possible, give the fear of error on the high side, that new recommended levels being currently decided by the U.S. Institute of Medicine, also discussed in this issue, will be too low to establish optimum blood levels of 25-hydroxyvitamin D.

This issue discusses the serious problem of vitamin A interfering with the action of vitamin D, the use of vitamin D in the treatment of chronic back pain and back pain that results from the very common failed back surgery, a remarkably flawed study of vitamin D and breast cancer which illustrates how not to design a randomized clinical trial, the use of vitamin D in treating depression and reducing the risk of colorectal adenomas. Given that there is some variation in how much vitamin D is required to build up 25-hydroxyvitamin D levels to optimum values, it can be argued that everyone should have their level of this compound measured, even if they live in southern latitudes.

The remainder of the newsletter deals with a variety of new results concerning hibiscus tea and tomato extract for blood pressure control, vitamin K for inflammation, and the failure of traditional risk factors for coronary heart disease to correlate with plaque burden. Finally, the risk of sudden cardiac death associated with antipsychotic drug use is discussed. This is a serious problem because these drugs are widely used by large numbers of individuals from young children to the elderly, and frequently for off-label indications. Do the benefits justify the risks?

***The Prostate Monitor** also appears in this issue. Individuals who are experiencing PSA progression after surgery or radiation treatment for prostate cancer should find this issue of particular interest.*

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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 good health,

William R. Ware, PhD, Editor

Highlights

VIEW OF VITAMIN D FROM GENEVA

It was reported in the press (*Globe and Mail*, Toronto, December 11, 2008) that the World Health Organization (WHO) through its cancer research agency The International Agency for Research on Cancer (IRAC) is calling for a major randomized clinical trial of the hypothesis that vitamin D plays a role in cancer prevention. They recognized that the data linking vitamin D and colorectal cancer was consistent and persuasive, that there was weaker evidence for breast cancer and that current data indicated little or no effect on prostate cancer. However, they took the common position that epidemiologic studies, while informative, have so often found promising effects with supplementation only to have clinical trials find no benefit. The IARC appeared particularly concerned regarding the question of whether low vitamin D status causes increased risk of cancer, other chronic health conditions and death or is simply a consequence of poor health status. The WHO interest in this subject may end up being counterproductive. Those dedicated to having their clinical practice influenced only by the highest level of evidence-based medicine may be encouraged to sit back and watch while some or many of their patients suffer from vitamin D deficiency, in some cases severe, and in most cases unmeasured.

In order to provide significant data, a randomized clinical trial with total cancer incidence and as well, various types of cancer as endpoints, would require a very large study group and to have much meaning would have to be conducted over a period of many years. One would hope that a number of endpoints not related to cancer would also be tracked. Given the extensive data supporting the notion that high vitamin D levels are critical to good health, perhaps the tens if not hundreds of million dollars might be spent on something more important within the context of the WHO mandate. At least some organizations are not waiting. The Canadian Cancer Society is recommending population-wide use of vitamin D and have taken the position that white individuals should take 1000 IU daily during the fall and winter and that dark skinned individuals should do this year-around. As discussed many times in this Newsletter, even 1000 IU per day may be insufficient.

INSTITUTE OF MEDICINE (U.S.) IS GETTING READY TO RECOMMEND NEW ADEQUATE INTAKE AND UPPER LIMITS OF VITAMIN D

The Institute of Medicine (IOM) has formed a committee to set recommendations regarding adequate intake of and upper limits for vitamin D.[1] In *The Vitamin D Newsletter*, concerns are raised regarding the composition of the committee. The major problem pointed out is the noteworthy absence of scientists who have been leaders in the so-called vitamin D revolution. Nevertheless, the committee does appear to have diversified experience in vitamin D related areas, and one individual was involved with the Woman's Health Initiative study. The *Vitamin D Newsletter* points out that this large and expensive study was noteworthy for simply showing that "meaningless doses of vitamin D are meaningless." The newsletter also points out that a number of the most distinguished vitamin D investigators just published a paper critical of the IOM and the related Food and Nutrition Board. This paper will be discussed below. The criticism centered on recommendations

regarding adequate intakes of vitamin D, the mandate of the new committee. And if past performance is any guide, the adequate levels of intake will be considerably lower if not vastly lower than currently recommended by the experts whose absence from the committee was noted.

VITAMIN A AND COD LIVER OIL INTERFERE WITH ACTION OF VITAMIN D

An important commentary on vitamin D has just appeared. The list of authors contains many well known vitamin D researchers and prominent nutritional epidemiologists.[2] This commentary by Cannell *et al* focus on the unfavourable interaction between vitamin D and either vitamin A or cod liver oil, a major source of the latter and a minor source of the former. This is an important issue since some multivitamin preparations can contain large amounts of vitamin A if taken as directed. Also, in keeping with the notion growing in popularity that grandma was right all along, cod liver oil is staging a comeback.

Evidence of the potential role of vitamin A in interfering with the action of vitamin D was provided by a comparison between recent results and results from the 1930s regarding the effectiveness of cod liver oil in preventing and treating upper respiratory infections. Recent studies have provided only very weak evidence of effectiveness with some studies indicating no benefit.

Studies reported in the 1930s found much more dramatic and convincing effectiveness. The authors suggest that this is due to much less vitamin D in modern cod liver oil. This suggestion was supported by studies in the last two decades where enhancing the vitamin D status of children resulted in pronounced decrease in respiratory infections. They also suggest that the resultant imbalance between A and D in modern cod liver oil further exacerbates the effectiveness of vitamin D since vitamin A interferes with the action of vitamin D.

Vitamin A and D compete for each other's function. Retinoic acid antagonizes the action of vitamin D and as well its active metabolite. As an example, Cannell *et al* point out that in humans the vitamin A in a single serving of liver is sufficient to impair the intestinal calcium response associated with vitamin D. In one study cited, high levels of retinol intake also completely eliminated the protective effect of vitamin D on colorectal adenomas and furthermore, there is evidence that the highest intake of vitamin D from supplements correlated with a high intake of retinol of about 10,000 IU/day. Cannell *et al* go on to comment that consumption of preformed retinol, i.e. that found for example in multivitamins, may cause bone toxicity in individuals with inadequate vitamin D status. Women in the highest quintile of total vitamin A intake have a 1.5 times elevated risk of fracture of the hip and in addition, a recent Cochrane Review found that vitamin A supplements increased total mortality rates and appear to increase the risk or worsen the clinical course of acute lower respiratory tract infections in children with normal vitamin D status.

Cannell *et al* present evidence that the relative amounts of vitamin D and A differ in modern cod liver oil vs. that used decades ago. Modern cod liver oil typically contains 400 to 1200 IU of vitamin D but supra-physiological amounts of preformed retinol (4000 to 10,000 IU and in some samples, 30,000 IU) per tablespoon have been noted. They theorize that modern processing intended to improve odor removes vitamin D which is then added back in lower quantities. Also, the amount of vitamin D in modern cod liver oil appears to be on the decline. They cite one manufacturer who produces cod liver oil containing only 3-60 IU of vitamin D per tablespoon but it contains 3000-6000 IU of vitamin A. Some individuals increase their intake of multivitamins simply to increase the vitamin D intake, and in the process can consume enough vitamin A to destroy the effectiveness of the vitamin D. Anyone depending on a multivitamin for part or all of their vitamin D, reading the label is obviously essential and may be surprising.

The message seems clear. Vitamin D3 supplements and sun exposure in the summer represent the appropriate approach to maintaining healthy vitamin D status. Adequate amounts are virtually impossible to obtain from diet. The article by Cannell *et al* also contains strong criticism of the so-called Adequate Intakes and Upper Levels of Vitamin D set by the U.S. Institute of Medicine's Food and Nutrition board, especially as regards pregnant women and children. As indicated above, this board is now in the process of revising these recommendations. The new numbers will be interesting.

VITAMIN D FOR CHRONIC BACK PAIN OR FAILED BACK SURGERY. SIX CASE STUDIES

While ignored by advocates of evidence-based medicine, case studies constitute an important first step in the process of forming a hypothesis regarding some benefit or risk in medicine. In a report by Gerry Schwalfenberg from the University of Alberta published in the *Journal of the American Board of Family Medicine*, a case series was recently presented that relates to the connection between back pain and vitamin D. This study involves 4 patients who had chronic back pain for more than a year and 2 patients who had suffered for more than 3 years from failed back surgery. This study reports the vitamin D status prior to treatment, i.e. the 25(OH)D levels, the vitamin D dose used and the 25(OH)D levels after repletion. In two cases it was necessary to estimate the vitamin D status prior to treatment. Patient descriptions at baseline and the symptom improvements were given. Four of the six patients had complete resolution of pain. In one case, when vitamin D treatment was stopped for several months, pain returned only to disappear again on restarting treatment. Two of the cases showed some improvement with one patient able to use less pain medication. In the cases where initial vitamin D status was measured, most patients exhibited very low status. Patients were treated with 1000 to 5000 IU/day and measured 25(OH)D levels increased into the normal or optimal range for all but two patients.

In spite of the limitations inherent to this type of study, the results should encourage individuals with chronic back pain, a neurological complaint reported to be second only to headache, to become concerned about their vitamin D status, have a 25(OH)D measurement done, and consider following the suggestion of vitamin D experts to increase supplemental intake to at least 2000 IU/day.

VITAMIN D AND BREAST CANCER

A large study designed to examine the connection between vitamin D supplementation and the risk of breast cancer has just reported.[3] Breast cancer was a secondary outcome of this randomized trial involving 1000 mg of calcium and 400 IU of vitamin D. A huge number of centers were involved. While the trial was placebo controlled, a rather unique aspect was that personal use of supplemental calcium and vitamin D were allowed in both the treatment and placebo groups. Using as an intervention 400 IU of vitamin a day but allowing up to 1000 IU a day in either the intervention or placebo groups constitutes a design feature that is odd to say the least. Also, most participants had 25(OH)D levels considered inadequate. For these reasons plus the fact that the levels of vitamin D supplementation used in this study bordered on insignificant, the results will not be discussed in detail and It would seem reasonable to simply ignore the conclusion that “These findings do not support a relationship between total vitamin D intake and 25-hydroxyvitamin D levels in breast cancer risk.” The defects of this study were clearly stated in an accompanying editorial which called for further trials with higher doses.[4]

VITAMIN D AND SYMPTOMS OF DEPRESSION

In a Norwegian study just reported in the *Journal of Internal Medicine*[5], Jorde *et al* examined the correlation between levels of depression measured with the Beck Depression Inventory method and vitamin D status measured by serum 25-hydroxyvitamin D levels (25(OH)D in over 400 overweight and obese individuals. It was found that subjects with 25(OH)D levels < 40 nmol/L scored significantly higher (more depressive traits) than those with levels ≥ 40 nmol/L. The subjects were then divided into three groups to receive either 40,000 IU of vitamin D3 week contained in two capsules, 20,000 IU plus a placebo, or two placebo capsules. In the two groups given vitamin D, there was significant improvement in depression scores after a year but no improvement in the placebo group. Also, there was an improvement in scores after vitamin D supplementation in both those with lower and higher baseline 25(OH)D levels, which is perhaps not surprising since the cut-off levels were

low compared to modern views on optimum vitamin D levels.

These results are consistent with a large study of over 1200 individuals, aged 65 to 95 years, published earlier this year.[6] This study found a significant association between depression status and 25(OH)D levels in both persons with minor depression and major depressive disorders. Approximately half of the subjects had 25(OH)D levels below 50 nmol/L.

In an editorial accompanying this second study,[7] it was suggested that the time has come for clinical trials on the antidepressant effects of vitamin D. The author cites two small trials, one with low levels of supplementation and one with UV light. Both indicated positive effects. To these should be added the above-discussed trial which also indicated positive results from intervention. While some would consider this enough evidence to try vitamin D therapy, others would demand a large intervention trial using significant amounts of vitamin D and careful monitoring of 25(OH)D levels. As the author points out, vitamin D is likely to be one of the most cost-effective treatments in psychiatry and one with negligible side effects. Thus the need for a large trial.

VITAMIN D AND COLORECTAL ADENOMA

A meta-analysis (study of pooled studies) concerning the relationship between serum 25-hydroxyvitamin D levels 25(OH)D and colorectal adenomas has just been published.[8] In an analysis of 17 studies, circulating 25(OH)D was inversely associated with the risk with an odds ratio of 0.7 and a 95% confidence interval of 0.56-0.87 when those with high vs. low circulating levels were compared. This corresponds to a 30% statistically significant relative risk reduction. Vitamin D intake was also inversely associated with colorectal adenoma recurrence. The authors conclude that these results further support the role of vitamin D in the prevention of colorectal cancer.

HIBISCUS TEA REDUCES BLOOD PRESSURE

Results of a small randomized trial showing that 3 cups of hibiscus tea daily for 6 weeks reduced systolic blood pressure SBP was presented at the American Heart Association 2008 Scientific Sessions and reported by Medscape Medical News (November 2008). The lead author was D. L. McKay from Tufts University. Among those with SBP over the median of 129 mm Hg, the reduction was almost 14 mm Hg whereas for those at or below 129 mm Hg, the SBP reduction on average was 7 mm Hg. This study was placebo controlled with insignificant, minimal changes in the placebo group. Dr. McKay pointed out that, on a population basis, a reduction of 3 mm Hg in SBP would be expected to yield a reduction in stroke mortality of 8%, of 5% in CHD mortality, and of 4% in all cause mortality, based on data in the literature. Thus reductions of 7 to 14r mm Hg appear important. There were no adverse effect and Dr. McKay pointed to the absence of adverse effects in Nigeria where a hibiscus-containing beverage equivalent to 25 cups of the tea used in this study produces no adverse effects. Hibiscus tea is available from health food stores.

VITAMIN K AND INFLAMMATION

The February issue of this Newsletter highlighted the connection between cardiovascular disease and inflammation. A recent paper in the *American Journal of Epidemiology* is highly relevant to this subject.[9] Shea *et al* obtained their data from the Framingham Offspring Study, enrolling 1381 subjects, mean age 59 years, 52% women. Data included alcohol use, diet information which allowed an estimate of vitamin K intake, medication use and for women menopausal status and hormone replacement therapy. Blood markers of inflammation as well as vitamin K and D status were obtained.

The estimated change in C-reactive protein (CRP), a marker for inflammation, was calculated for a twofold change in vitamin K status estimated with three blood markers. At enrolment, the mean CRP level was 3.8 mg/L with a standard deviation of 5.3 and a range of 0.2 to 66.2 mg/L. For a twofold

change in vitamin K status, the estimated change in CRP was between 0.92 and 0.85 mg/L. Of the 14 inflammation markers examined, this change in vitamin K status had a statistically significant impact on 8 as judged by one or more assays of vitamin K status. A twofold change in vitamin D status did not produce a statistically significant change in CRP levels.

The "K" in vitamin K stands for koagulation, the Danish spelling of the blood clotting process that cannot occur without this micronutrient. Intestinal bacteria can make this vitamin and it is obtained in the diet from green leafy vegetables. It is also involved in the formation of osteocalcin, the structural framework inside bones around which calcium crystals form. Low levels are frequently found in women with osteoporosis. Supplementation is of course contraindicated if one is on anticoagulant drugs. Eating kale, parsley and green leafy vegetables radishes, cabbage, broccoli, spinach, beans and asparagus will provide vitamin K and eggs also contain some. Presumably the monitoring that accompanies the use of such drugs, as Coumadin will pick up a problem if excessive vitamin K intake from food is present. Sinatra in his book *Reverse Heart Disease Now* [10] has expressed concern about vitamin K deficiencies in individuals who are on such drugs as Coumadin, especially for extended periods or for life, since if they are advised to avoid the above listed foods, they could develop a severe vitamin K deficiency which would carry increased bone and heart risks. There are actually two forms of vitamin K, i.e. K-1 and K-2. It is K-1 that is present in the foods listed above. Vitamin K-2 is also associated with bone health and higher intakes have been related to reduce artery calcification. It is far less abundant in food but is found in the Japanese fermented soy food called natto as well as in fermented and curded cheese. The same contraindications apply as with K-1.

TOMATO EXTRACT REDUCES BLOOD PRESSURE

Two papers from Israel have now appeared which employed a tomato extract in capsule form to lower blood pressure. The first was a pilot study on untreated hypertensives which appeared in 2005.[11] This has now been followed by a study of the use of this extract on uncontrolled hypertensives.[12] In the study on untreated hypertensives, systolic blood pressure (SBP) decreased from 144 to 134 mm Hg and diastolic blood pressure (DBP) decreased from 87.4 to 83.4. These are mean values for 31 patients and were compared to a placebo phase with the same group where there was no significant change in blood pressure. In the second study, 50 subjects with moderate hypertension being treated with one or two antihypertensive drugs were entered into a double blind cross-over program with two periods of 6 weeks. At the end of the 6 weeks period, the tomato extract group was switched to the placebo, and the placebo switched to the tomato extract. Those on the tomato extract had a decrease in blood pressure which then rose back to near baseline when they went on the placebo, The reverse occurred when blood pressure remained constant during the placebo phase and then declined on the tomato extract. The mean declines in SBP were from 145.8 to 132.2 and 140.4 to 128.7 mm Hg. Mean declines in DBP were from 82.1 to 77.9 and 80.1 to 74.2 mm. Hg. Serum lycopene, one of the proposed active ingredients in tomatoes tripled after tomato paste therapy. There was a significant correlation between SPB and lycopene levels.

The tomato extract was a commercial preparation (Lyc-O-Mato). The dose was 250 mg/day. Each capsule contains 15 mg of lycopene plus a number of other phytochemicals. However, the nature of the trial did not allow the identification of the active ingredient. No side effects were observed in either study.

These studies are certainly hypothesis generating. When one looks at the literature to see if anyone has tried the same type of study with just lycopene alone, there do not appear to be any such studies. It is curious, however, that one study in 2007 looked at lycopene derived from cooked tomatoes on lipid peroxidation in hypertensives but did not report any blood pressure data.

One large tomato (200g) contains about 13 mg of lycopene. However, the bioavailability is thought to be considerably less than that from tomato paste or sauce. A cup of tomato soup contains about 25 mg, a half-cup of tomato or spaghetti sauce, about 20 mg. A large slice of watermelon would provide about 15 mg. Bioavailability is enhanced by including fat in meals rich in lycopene. The average daily dietary consumption has been estimated at about 25 mg.[13] The capsules used in the above

studies contained 15 mg of lycopene and the dose was one a day. Thus if lycopene is the active ingredient, it is a bit odd that adding only 15 mg/day would have such a large effect.

Another way of looking at this study is to compare the blood lycopene levels with other groups. In the two studies discussed above, the plasma levels were about 0.1 microgram/L. In a study of over 3000 Europeans from 16 regions (the EPIC study), the average was 0.74 ± 0,42 with no value below 0.3 micrograms/L. Thus for some reason, the groups studied using the tomato extract supplement had quite low starting levels which were only brought up to the lower end of the EPIC study at the end of the supplementation period. Thus this approach to blood pressure lowering needs to be tested on a more normal cohort. Furthermore, it is far from clear that lycopene is the active ingredient in terms of blood pressure lowering and that taking supplemental lycopene or Lyc-O-Mato, while an interesting experiment that "can be tried at home" may not have the effects observed in this cohort from Israel.

TRADITIONAL RISK FACTORS FAIL TO CORRELATE WITH CORONARY PLAQUE BURDEN

A paper has just been published by Johnson *et al*[14] which strengthens the view that the traditional assessment of coronary heart disease risk leaves much to be desired. This study employed a more sophisticated CT scan which identified all plaque, not just calcified plaque. Only about 20% of plaque is calcified and represented by the Coronary Artery Calcium Score. This is important, at least in a research setting. The technique used is called contrast-enhanced CT angiography (CTA). Over 1600 patients underwent CTA (34% women). Mean ages for men and women were 52 and 57 years, respectively. The most common reasons for the examination were high cholesterol, family history, hypertension, and smoking and atypical chest pain. All were classified according to the standard Framingham risk score (FRS) and the protocol of the National Cholesterol Education Program (NCEP ATP III) which determines the level of risk by counting risk factors in addition to the FRS. For the NCEP evaluation, one ends up with four categories, low, intermediate, moderately high and high risk. The details and calculators can be found at a number of different websites. In the cohort studied, the low, intermediate, moderately high and high risk groups comprised 50%, 15%, 20% and 15% of the total group for men, and 56%, 23%, 8% and 13% for women, respectively. Statin use was 44% for men, 45% for women. Patients with a history of heart disease were excluded. Diabetics made up only a small percentage of the subjects.

Since four different plaque-scoring protocols were used, to keep this discussion simple, only the general conclusions will be reviewed. While median plaque scores increase significantly from lower risk to higher risk categories, the investigators found that the variance was large, which presented a problem for clinical use. The four measures of plaque burden correlated poorly with the conventional risk stratification. If the risk factor approach (NCEP) was used, many patients with little or no plaque would be subjected to lifelong drug (statin) therapy, whereas many with substantial plaque would be underrated or not treated at all. Whether in this cohort treatment would offer significant benefit was obviously not discussed, but has been extensively discussed in research reviews in this Newsletter. More than 25% of patients on statins had no detectable plaque but were destined to be on drug therapy for life. More than one in 10 patients with no visible plaque were deemed to be of moderately high or high risk according to NCEP and 32% of patients with no detectable plaque were taking statins. When using plaque burden as a standard measure of risk, traditional risk factor analysis misclassified more than half of the patients. The researchers also examined the correlation between total cholesterol and plaque burden and found none. This agrees with studies using calcium scores which also find no correlation, a disturbing observation if one believes that elevated blood cholesterol causes atherosclerosis.

In an interview with *theheart.org* the lead author pointed out that studies linking the findings from CTA to clinical outcomes have not been completed. But he admits that it is widely accepted that the more plaque you have, the worse it is for you. This certainly is the case with the partial plaque analysis provided by the calcium scan. Johnson's caveat also ignored the results of Min *et al*[15] who with the same CT technique found that in patients with chest pain, CTA identifies increased risk for all-cause death and a negative CTA indicated an extremely

low risk of death. That study involved 1127patients ≥ 45 years old with chest symptoms.

The authors conclude that coronary CTA may provide incremental information beyond risk factors and may significantly influence therapeutic decisions regarding preventive therapy for coronary heart disease. This seems like an understatement, given the poor performance of traditional risk factors observed and the large number of patients on statin drugs when, according to the views of most, their zero plaque burden means an insignificant risk of a CHD event. However, it is unlikely that CTA will become a routine screening tool. It requires injection of an iodine containing contrast material whereas ordinary calcium scanning does not. Nevertheless, these results are important because they expose a significant weakness in the risk assessment protocol used worldwide which is for many the gateway to lifelong statin use. In fact, what is really at issue here seems to be the question of to what extent the actual state of the coronary arteries should be investigated before life-long medication is started. The currently used approach to risk assessment appears to not be that much concerned with the life-long aspect of statin therapy. This might be satisfactory if the drugs were totally free of side effects, but this is not true and in fact finding the true extent of statin side effects is now being actively studied, especially at the University of California, San Diego.

ANTIPSYCHOTIC DRUGS ASSOCIATED WITH SUDDEN CARDIAC DEATH

Extensive data link typical antipsychotic drugs to an increased risk of sudden cardiac death (SCD). A study has just been published which examines this problem in individuals taking so-called atypical antipsychotic drugs which have largely replaced the older agents in clinical practice, partly because they are less likely to cause serious movement disorders.

Typical Drugs

- haloperidol (Haldol)
- thioridazine (Mellaril)

Atypical Drugs

- clozapine (Clozaril)
- olanzapine (Zyprexa)
- quetiapine (Serofquel)
- risperidone (Risperdal)

Some of these drugs have other trade names. Antipsychotic drugs are commonly used across the entire age spectrum, both within and outside their labelled (and evidence-based) indications. Three of the four atypical drugs listed above are among the top-selling drugs worldwide with combined sales volume of $14.5 billion.[16]

Ray *et al*[17] have performed a retrospective cohort study of Medicade enrollees in Tennessee. Approximately 44,000 and 46,000 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonusers of antipsychotic drugs were studied.

When the incidence of SCD was compared, typical and atypical drugs had similar enhanced risks and there was a strong dose-dependence in both classes. High doses resulted in more than doubling the risk in comparison to nonusers with the incidence rate ratio reaching almost 3 times for high-dose atypical drugs. The investigators controlled for an extensive set of cardiovascular disease variables in their analysis. It is well known that long-term adverse cardiovascular effects are associated with antipsychotic drugs, but since the risk of sudden death is elevated even when long-term users are exclude, this suggests that acute drug effects are involved. The authors state that in their opinion, the most plausible explanation for the enhanced risk of SCD is that antipsychotic drugs increase the risk of serious ventricular arrhythmias, probably through blockage of potassium channels.

In an editorial that accompanied the paper by Ray *et al,* Schneeweiss and Avron[16] discuss the serious risk issues involved in the use of this class of drug, commenting that a thorough evaluation is particularly important since they are so frequently used and in such diverse patients, many of whom are children and the elderly. The point out that it is striking that it took so long to establish elevated risk associated with atypical antipsychotic medication given that clozapine, the first member of the class, came on the market in 1989. In addressing the question of whether or not the use of these drugs should be restricted on the basis of the data presented by Ray *et al*, they point out that much of their use is outside of labelled indications, in particular in children and in the elderly with

dementia, and there is much less evidence of efficacy in these populations. Thus they suggest that in the absence of clearly established benefits for many of these patients, the risk of fatal side effects is not likely to be acceptable. They also comment on the prevalence of SCD among adults treated with these medications. Overall in the population studied by Ray *et al,* higher doses had a rate of 3.3 events per 1000 which they regard as not "rare." They also comment on the well established risk-management program that has been in place for almost two decades for clozapine associated agranulocytosis (an acute condition characterized by a drop in white cell count, fever, and potentially septicaemia, which has been reported to occur at a rate of about 7 per 1000 users) which requires monitoring of white cell counts prior to refilling a prescription. They suggest a similar program which would screen patients prior to starting high-dose antipsychotic drugs which would involve electrocardiographic screening for existing or emergent irregularities.

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The Prostate Monitor
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Reviews of recent studies from the peer-reviewed literature

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As reported earlier in The Prostate Monitor, studies from the University of California at Los Angeles (UCLA) found that pomegranate juice had the potential for slowing, arresting or reversing the progression of PSA associated with the recurrence of treated prostate cancer. In this issue an encouraging update of that study is presented. When your editor became aware of the UCLA work he passed it on to an acquaintance who was experiencing alarming PSA progression after failed salvage radiation therapy intended to solve the problem of recurrence of his prostate cancer subsequent to a radical prostatectomy. In January 2007 this individual started drinking 8 oz of pomegranate juice daily, using the brand employed in the UCLA studies which was available at his local supermarket. Prostate Monitor provided a preliminary report a few months later that was very encouraging. Now we are able to provide a history over about 2 years which is unique in that it involves PSA measurements every few months, something not done normally outside of clinical studies. Readers of the Prostate Monitor who have biological recurrence (PSA progression) after surgery or radiation for prostate cancer should find this case history of considerable interest, in sharp contrast to one of the physicians involved in the care of this individual who was not at all interested in what was being done to prevent what is almost always the inevitable progression to metastatic cancer, even though he was told the approach was supported by research from UCLA! After all, the notion that something the supermarket sells in little funny-shaped bottles may solve one of the most serious problems in prostate cancer therapy is of course, a priori, wild and dangerous nonsense. A review of research is also discussed below which is directed at understanding the mechanism of action of pomegranate juice or its extract on prostate cancer cells. It also comes from the same UCLA research group. All this work is published in respected peer-reviewed journals or presented at major oncology conferences. The supermarket sells the juice for the obvious reason that it tastes good and presumably is not dangerous to drink. It was once called the beverage of millionaires, but the price has obviously come down quite a bit.

In this issue we also review progress on the problem of vitamin D and prostate cancer, in this case, disease related mortality. In addition, the recurrent subject of the utility of PSA in establishing the presence and nature of prostate cancer is examined again in the light of a new analysis of data from the Prostate Cancer Prevention Trial. Readers will recall that this trial suggested that Proscar used to treat BPH appeared to significantly prevent the incidence of prostate cancer, and that the suggestion that Proscar increased the risk of advanced cancer appears to be an artefact. But the placebo arm of the trial was equally interesting since it allowed the examination via biopsy of (more or less) the real state of affairs in the prostate as a function of the PSA level for a large number of individuals with PSA < 3 ng/mL at baseline and < 4 ng/mL at biopsy, with no evidence of the disease. The study population includes the whole range of PSA down to < 1.0 ng/mL. An obvious conclusion from this study is that there is a desperate need to replaced PSA with a test that is not plagued by false positives and false negatives. What investigators in this field seem reluctant to comment on is that the biopsy also misses a significant number of cancers. The problems with prostate biopsies as well as the Prostate Cancer Prevention Trial and PSA as a diagnostics tool are discussed in our book, "The Prostate and its Problems". Knowledge in

this field is important to all men being offered a PSA test since the true state of affairs may not be made clear during the brief discussion that precedes checking off the PSA box on the blood test form.

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

UPDATE ON POMEGRANATE JUICE AND PROSTATE CANCER

In the Prostate Monitor of May, 2007, a study was discussed which found that drinking pomegranate juice dramatically increased the PSA doubling time (PSADT) for men with rising PSA after surgical or radiation treatment for prostate cancer.[1,2] This study has been continued and patients remaining in the study continue to show a durable increase in the PSADT as of August 2007. Patients remaining in the study (active) were compared with those who no longer in the study (non-active). At baseline, the active and non-active patients had similar PSA doubling times. The mean post treatment PSADT increased in the non-active patients to 51 months, but the for the active patients, it increased to 69 months.[3] The conference abstract from which this information was derived does not indicate how many of the non-active patients still drank pomegranate juice. The authors conclude that this research reaffirms the positive results of the earlier trial by showing that the beneficial effects of pomegranate juice on PSADTs in this clinical setting can be long-term.

UPDATE ON A CASE HISTORY OF THE USE OF POMEGRANATE JUICE FOR RISING PSA

In the July-August 2007 Prostate Monitor a case history was presented that related to the ability of pomegranate juice to influence PSA-only recurrence. The information and what follows was obtained from a friend who had undergone a radical prostatectomy in June 1997 at age 65. He suffered so-called biochemical recurrence and by February 2004 his PSA had advanced to 0.95 ng/mL with a doubling time of less than 2 years. In the language of the layman, they did not get it all. He elected salvage radiation therapy which produced a nadir of 0.12 ng/mL by December 2005, but this was not durable and his PSA started increasing exponentially and reached 0.37 by Jan 2007 with a doubling time of 7.9 months based on three determinations. At this point he started taking pomegranate juice (POM from POM Wonderful Co), one glass per day. It is now possible to update this history with 2 years of results while this individual has been taking pomegranate juice.

Date	PSA (ng/mL)
January 3, 2007	0.37 - Pomegranate juice started
April 20, 2007	0.24
May 15, 2007	0.24
November 6, 2007	0.55
January 16, 2008	0.54
May 15, 2008	0.55
October 22, 2008	0.61
December 6, 2008	0.56
February 10, 2009	0.61

All of the PSA determinations were made at the same laboratory. This case in unusual in the number of serial PSA determinations that were done since the individual was not part of a study. Thus over a period of more than a year his PSA has been stable and while the low value of 0.24 was not maintained, there was a rapid rise to a long plateau of between 0.55 and 0.61. When PSA values increase after the nadir achieved by salvage radiation therapy, it generally means that the radiation field did not encompass the sites where there were prostate cancer cells or that the intensity was too low, or both. Normally once it starts, especially when the doubling time is

about 8 months, the progression of PSA simply continues, and at some point, hormone therapy becomes a topic for discussion. Salvage radiation therapy did not work. If the doubling time of 7.9 months prior to the start of the pomegranate juice therapy had been maintained, the PSA now would be over 3.0 rather than O.61 ng/mL.

After the PSA had reached the plateau, i.e. starting at November 6, 2007, the resultant doubling time is about 100 months or about 8.4 years, which is even better than the average found in the studies form UCLA. In fact, the plateau can be interpreted as simply a constant PSA with minor fluctuations. Some urologists who advocate intermittent hormone therapy use 10 or 20 ng/mL as the threshold for starting treatment. At a doubling rate of 8 years, to get to a PSA of 10 starting at 0.6 would require about 35 years at which point this individual would be well over 100 years old.

At the present time, most urologists would probably consider this individual of low risk for symptomatic metastatic prostate cancer, or at least of dying from prostate cancer (see the May 2007 issue of the Prostate Monitor). However it is an open question as to whether the slowed or arrested PSA progression can be interpreted in this manner since it is always possible that there may be some other explanation for the low PSA values that does not indicate an arrested or slowed progression of the disease, but only the marker. However, this possibility seems remote and the individual in question is quite likely to be “out of the woods” for good.

While this is just one case study, when considered along with the data from the University of California at Los Angeles which was discussed above, it seems clear that this approach may have merit, especially when the drink is pleasant, was called the beverage of millionaires, and if there are side effects, no one has seen them yet, and this includes the decades when the juice was consumed for pleasure, not PSA control.

It would be interesting to see if the pomegranate extract, which is now available from the same company that makes the juice used in the clinical studies (POMX from POM Wonderful), would for the individual whose data is displayed above maintain current levels or even decrease them. The extract makes it easy to take a higher dose of potentially active ingredients which might have an even bigger impact. One POMX capsule is equivalent to 8 oz of pomegranate juice. Incidentally, the company name “Wonderful” refers to the variety of pomegranate used for their products, not their self-perception. Other companies also make a pomegranate extract marketed in capsules and there are other vendors of the juice. However, only products from POM Wonderful have been used in studies. Researchers at UCLA indicate that POMx and POM juice have the same effects on prostate cancer.[4] Incidentally, as discussed in the July/August 2007 Prostate Monitor, there appears to be no basis for concerns that pomegranate juice or extracts might interfere with drug clearance in the same way that is seen with grapefruit juice.

Finally, when pomegranate fails to control the progression, which may indeed happen, the Salvestrols described in an earlier Newsletter represent another potentially beneficial therapy, and more data regarding this interesting approach is awaited with considerable interest. The paper describing the case studies involving Salvestrols discussed in the June 2008 issue of the Newsletter is now available free online at
http://www.lifebeyondterminal.com/storage/JOM%20case%20studies%20december%202007.pdf
Unfortunately, the prostate cancer case study, while very encouraging, did not involve a long enough follow-up after the patient was taken off hormone therapy to see if the Salvestrol alone was enough. A case involving Salvestrol treatment reported on the Internet was effective only for less than a year. In this case the individual had metastatic cancer and had been given only 5 years to live. The story can be found at http://www.sohumone.com/Health.htmL. In addition, it appears that the formulation has been improved since these case-study reports appeared.

Readers interested in trying Salvestrols are encouraged to contact the company for up-to-date information for particular sites. Their website is http://www.salvestrol.ca/index.asp. The company also provides information for practitioners.

POTENTIAL MECHANISMS FOR ACTION OF POMEGRANATE JUICE AND EXTRACTS ON PROSTATE CANCER

Three papers have just appeared from the UCLA group responsible for the studies discussed above concerning pomegranate juice and PSA doubling times. In one study the researchers demonstrated that pomegranate extract (POMX) inhibited one of the most well-established signaling pathways mediating inflammatory responses related to cancer, the nuclear factor-kappaB (NF-κB) pathway. Pomegranate extract (PE) inhibited the NF-κB pathway and cell viability of prostate cancer cell lines in a dose dependent fashion *in vitro*. Maximal PE-induced cell death was dependent on NF-κB blockage. Furthermore, the researchers investigated the inhibition of proliferation and the induction of cell death in a mouse model of prostate cancer and found that PE delayed the emergence of implanted tumor cells in castrated mice. In addition, the increased NF-κB activity during the transition from androgen (hormone) dependence to androgen independence in this model was abrogated by PE. The authors conclude that PE is a promising dietary agent for the prevention of hormone independent prostate cancer that is driven in part by heightened NF-κB activity.[5]

A second study examined the impact of PE on angiogenesis (development of blood supply) which is critical for tumor growth. In cell culture studies and mouse studies, it was demonstrated that PE can inhibit tumor associated angiogenesis and that this is one of several potential mechanisms for slowing the growth of prostate cancer in the chemopreventive setting.[6]

The third paper concerns the ability of pomegranate polyphenols to down-regulate the expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor.[7] When prostate tumors progress to the androgen-independent state they progress in the absence of circulating testosterone which eliminates the effectiveness of hormone therapy. During the development of this hormone-independent progression, it is know that prostate cancer cells increase intracellular testosterone synthesis which maintains cancer cell growth in the absence of significant amounts of circulating testosterone caused by hormone therapy. Over expression of the androgen receptor occurs in androgen-independent prostate cancer and has been proposed as another mechanism whereby the development of androgen independence occurs. This study demonstrated that pomegranate polyphenols inhibited androgen-synthesizing enzymes and the androgen receptors and this may be particularly important in androgen-independent prostate cancer cells and prostate cancer cells where the androgen receptors are up-regulated.

Thus there appears to be rapid progress in identifying possible mechanisms whereby the phytochemicals and in particular the polyphenols in pomegranate juice and its extract inhibit the progression of this disease.

VITAMIN D AND PROSTATE CANCER MORTALITY

Vitamin D does not appear to influence the incidence of prostate cancer and there is weak evidence that high levels of 25-hydroxyvitam D (25(OH)D) may even correlate with the incidence of more aggressive forms of the disease, although a clear monotonic dose-response is lacking.[8] However, vitamin D levels as measured by 25(OH)D appear to be strongly inversely correlated with progression and mortality associated with established disease. A study just published from Norway addresses this issue.[9] This study involved 160 patients of which 97 were on hormone therapy. During the follow-up which had a mean time of 44 months (range 1.2 to 155), 61 patients died, the majority from prostate cancer. The vitamin D status was stratified according to low (< 50 nmol/L), medium (50-80 nmol/L and high (> 80 nmol/L) of 25(OH)D. The results were analyzed according to several models, with the model which included age, tumor grade (differentiation) and patient functional status at the time of blood collection giving the strongest correlation between mortality from prostate cancer and vitamin D status, When those in the medium and high levels were compared to those with a low level of 25(OH)D, statistically significant risk reductions in prostate cancer-specific mortality of 67% and 84% respectively were found. When the analysis was restricted to patients receiving hormone therapy, the association was even stronger. It was concluded that the serum level of 25(OH)D may be involved in disease progression and is a potential marker of prognosis in patients with prostate cancer.

It is possible that the mechanism providing this benefit may involve a transcription factor called Stat3 which in active in malignant prostate cancer.[10] Grant has pointed out that vitamin D has been found to inhibit the action of Stat3 and increase cancer cell death and invasion and metastasis.[11] It is also possible that the metabolite of 25(OH)D, 1,25-dihydroxyvitamin D is involved since it is known that prostate cancer cells contain the required

enzyme to convert 25(OH)D to this metabolite. Grant points out that making sure that those diagnosed with prostate cancer have high 25(OH)D levels may be important for this reason.

PSA AND RISK OF PROSTATE CANCER

In a landmark study by Thompson *et al* published in 2004, 2950 men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) underwent end-of-study prostate biopsies regardless of PSA and digital rectal examination (DRE) findings. For those with PSA ≤ 4.0 ng/mL at the time of biopsy, about 15% were diagnosed with cancer. The risk increased with PSA levels but was present at even low levels. One critical question concerns the prevalence of insignificant cancers found at biopsy and in the pathological examination of prostates surgically removed. The PCPT data has now been analyzed to examine this question.[12]

PSA categories were 0-1.0, 1.1-2.5, 2.6-4. Tumors found at biopsy were categorized as potentially insignificant if they were stage T1c (detected by elevated PSA), negative DRE, PSA density < 0.15 ng/mL/g, and no evidence of Gleason pattern 4 or 5 in the biopsy cores, Gleason score ≤6, tumor limited to < 3 cores with no more than 50% involvement of any core. A second similar set of criteria were also applied. With the above definition of insignificant, the percentages of cancer meeting the criteria for the three strata of PSA were 51.7%, 33.7% and 17.8%. In the PSA range from 0 to 2.5, 39% had insignificant cancer or put another way 61% has significant cancer. The percentages of detected cancers that were significant increased with PSA level and for those with 2.6-4.0 mg/dL, the number was over 82%. These figures did not change much when the data is restricted to the placebo group with a normal DRE.[13]

A subgroup underwent radical prostatectomy. Adverse pathology observed on the prostates removed surgically was defined as any of the following: Gleason score of ≥7, extraprostatic extension, seminal vesicle invasion, positive surgical margin, or lymph node metastasis. In men with PSA between 1.1 and 2.5, 37.9% had one or more adverse pathologic features and this increased to 49.1% for the group between 2.6 and 4.0 mg/dL. Extraprostatic extension went up strongly with PSA, as did positive surgical margins. Even when the PSA was below 1.0, 15% had one adverse feature (in this case a Gleason ≥7). The presence of adverse pathologic features indicates an enhanced risk of treatment failure.

These results strengthen the view that there is no cut-off value for PSA that can provide a high level of comfort if one is worried about having prostate cancer. Furthermore, the real risk of significant disease and disease with adverse features increased monotonically with PSA with no apparent threshold. These results also support the view that the only way to answer the question of the presence of prostate cancer is with a biopsy. But even this statement needs qualification since biopsies also miss cancers. The need for a simple diagnostic test for prostate cancer with a high level of sensitivity and specificity appears urgent. Those who think it is the PSA test are misguided or deceived. The multitude of problems associated with the diagnosis of prostate cancer are discussed in our book *The Prostate and Its Problems. A Guide to Conventional and Alternative Prevention and Treatment.*

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