

# INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 187

MAY 2008

17<sup>th</sup> YEAR



*This issue features two related health problems, the metabolic syndrome and cardiovascular disease. Both are distressingly prevalent and in addition are the subjects of a vast amount of clinical and laboratory research, both past and ongoing. Putting "metabolic syndrome" as a title item into the U.S. National Library of Medicine's powerful search engine (referred to by users simply as PubMed) brings up over 1250 citations for just the past 12 months. Gerald Reaven popularized the concept of the clustering of insulin resistance, a dyslipidemia characterized by elevated triglycerides and low HDL cholesterol, and hypertension in his 1988 Banting Lecture and in addition alerted the general public to the dangers of the syndrome in a book titled "Syndrome X" which appeared in 2000. The presence of the metabolic syndrome vastly increases the risk of coronary heart disease and diabetes, is easily diagnosed, and unfortunately is highly prevalent in populations characterized by large numbers of overweight and obese individuals. The presence of the individual components of the syndrome themselves constitute risk factors for coronary heart disease, should be taken very seriously, and in fact according to some experts, should be treated independently even if only one or two are present and the metabolic syndrome is absent, i.e. fewer than three of the components required in the definition are present.*

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*Wishing you good health,*

**William R. Ware, PhD, Editor**

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The diet pattern associated with the traditional Mediterranean diet as consumed for example in Greece 40-50 years ago has been found in a

number of studies to represent an optimum diet in the context of the primary prevention of both cardiovascular disease and diabetes. In general terms, the diet is characterized by a high consumption of fruits, vegetables, legumes, whole grains, moderate alcohol intake, moderate to low consumption of dairy products and meats, and a high ratio of monosaturated to saturated fat. Olive oil is an important source of fat, and moderate amounts of alcohol are generally consumed with meals. In what follows, we briefly review some recent studies of interest in connection with cardiovascular disease.

## **MEDITERRANEAN DIET IMPROVES SURVIVAL AFTER HEART ATTACK**

The Mediterranean diet is associated with lower incidence of coronary heart disease and appears to improve prognosis of coronary patients, although many of the studies addressing this question have been of limited power. A recent study from Greece evaluated the association of adherence to a modified Mediterranean diet and survival among elderly patients with a previous heart attack. Participants were 60 years or older and were followed for almost 7 years. A 10-point scale was used to assess adherence to a modified Mediterranean diet in which unsaturated fats were substituted for monosaturates. Otherwise, the components identified with the Mediterranean

pattern were vegetables, legumes fruits, nuts, cereal and fish, and alcohol. The scoring system took into account the ratio of saturated to unsaturated fat and the consumption of meat and dairy products. The score ran from zero to 10 and the higher the number the closer the diet corresponded to what the investigators considered to be the ideal modified Mediterranean diet. It was found that for every 2-point increase in the score, there was a 18% lower overall mortality and that closer adherence, as indicated by an increase of 4-points on the 10-point scale, reduced the risk of death overall by 33% in this cohort of patients with a previous heart attack.<sup>1</sup>

## **MEDITERRANEAN DIET REDUCES INCIDENCE OF METABOLIC SYNDROME**

A Spanish prospective cohort study has just reported on the impact of a Mediterranean diet on the incidence of the metabolic syndrome with a follow-up of up to six years. An adherence score similar to that described above was used. The Mediterranean diet pattern characterized by the researches was similar to that given above. Participants were young, recent graduates and but could not have exceptionally high values for energy intake, a BMI > 30 kg/m<sup>2</sup>, or risk factors such as diabetes, elevated cholesterol, high blood pressure, or elevated triglycerides. When individuals with a score of 0-2 were compared with those having a score of 6-9, the risk reduction for being characterized as having developed the metabolic syndrome was 80%. This result was statistically significant and was adjusted for a number of potential confounders. The authors comment that this is the first prospective study to provide evidence that the Mediterranean diet provides protection against developing the metabolic syndrome, which also means a significant reduction of in the risk for developing cardiovascular disease and type 2 diabetes.<sup>2</sup>

## **SYSTEMIC INFLAMMATION AND THE MEDITERRANEAN DIET**

Inflammation is considered one of the causative factors for atherosclerosis which can operate over a number of years to initiate and then influence the progression of atherosclerosis. Preventing systemic inflammation, identifying its presence and attempting to reduce it should be essential features of any primary prevention program. Thus the obvious question, are there dietary components or patterns that are inflammatory or non-inflammatory or anti-inflammatory? Two studies have appeared recently that relate to this question. In one, circulating markers of systemic inflammation were studied as a function of adherence to a Mediterranean diet pattern. Subjects were involved in the Twins Heart Study. Dietary information was collected with a questionnaire and the serum levels of inflammation markers as well as blood lipids and fasting glucose were determined during the

examination of candidates for participation. It was found that adherence to the Mediterranean diet pattern was associated with reduced levels of interleukin-6 and C-reactive protein (CRP) but after adjustment for potential confounders, only the association with interleukin-6 was statistically significant. By comparisons between and within twin pairs, it was concluded that shared environment and genetic factors were unlikely to play a major role in this association between diet and this marker for inflammation. The authors comment that these results support the hypothesis that reduced inflammation is an important mechanism linking the Mediterranean diet to reduced cardiovascular risk. CRP was associated with the adherence score in the model prior to adjustment, and it is not clear how meaningful the adjustments are in this case since CRP has a strong association with

cardiovascular risk which is also attenuated by adjusting for confounding factors. The authors suggest that interleukin-6 may be a more sensitive inflammation marker.<sup>3</sup>

The second study investigated the association between two micronutrients, choline and betaine, and inflammatory markers in healthy adults.<sup>4</sup> Intake of both is enhanced in the Mediterranean diet. Participants in this large study had no history of cardiovascular or any other atherosclerotic disease, no chronic viral infections, cold, or flu, no acute respiratory infections and no dental problem, all potential causes of elevated inflammation markers. It was found that those with high intakes of choline and/or betaine had lower serum levels of C-reactive

protein, interleukin-6, and tumor necrosis factor-alpha. These markers are believed to be significantly associated with the risk of cardiovascular disease. The findings were independent of various socio-demographic, lifestyle and clinical characteristics of the participants. These effects of dietary choline and betaine on inflammatory markers were of the same magnitude as those reported for the Mediterranean diet. Choline is found in eggs, pork, beef, and fish. Plant sources include beans, tofu, almonds, peanuts, oat bran, Brussels sprouts, broccoli and cauliflower. Betaine, which is a derivative of choline, can be found in wheat germ, spinach, shrimp and mushrooms.

## **METABOLIC SYNDROME BUT NOT FRAMINGHAM RISK SCORE PREDICTS ACUTE CORONARY SYNDROMES**

A recent study from Greece has examined the ability of the European Risk SCORE and the Framingham Risk Score (FRS) as compared to the presence of the metabolic syndrome in predicting the risk of acute coronary syndromes (ACS) in young adults aged < 45.<sup>5</sup> Two hundred consecutive patients (92% men) hospitalized for a heart attack or unstable angina (chest pains) were age- and sex-matched with controls. Metabolic syndrome was defined as abdominal obesity (waist circumference > 102 cm for men and >88 cm for women), triglyceride levels > 149 mg/dL, HDL levels < 40 mg/dL (men) and < 50 mg/dL (women), fasting blood glucose > 99 mg/dL and hypertension ( $\geq$  130/85 or treatment for hypertension). The odds of having ACS were almost double for those with the metabolic syndrome even after adjusting for hypertension, family history of premature CHD, smoking, fasting glucose and blood lipid levels.

There was no significant association of the risk of ACS and the FRS, even after adjusting for confounding. Also, the European SCORE gave  $\leq$  1% risk for both the ACS patients and controls. Patients with 4 or 5 metabolic syndrome characteristics had an almost 4 fold increase risk of ACS compared to those not having the metabolic syndrome. It is of interest that while the Framingham Risk Score has been found to overestimate CHD risk in low-risk southern European populations, in this study it failed completely to distinguish those at risk of ACS. The authors conclude that the diagnosis of the metabolic syndrome provides an important tool for prevention in individuals with apparently low to moderate risk according to the FRS. It is also of significance that these results are consistent with studies that find no correlation between the FRS and the extent of atherosclerosis as measured by coronary calcium.

## **ENDOTHELIAL FUNCTION AND THE METABOLIC SYNDROME**

A recent study from the UK has examined the role of the metabolic syndrome as defined above and endothelial function as measured in the brachial artery in the arm by an ultrasonographic technique that involved measuring the recovery after artificial occlusion with a cuff.<sup>6</sup> This technique allows the quantification of endothelial dysfunction, a disorder which is a key step in the initiation and progression of atherosclerosis. Participants were asymptomatic, age in the mid 30s, with no previous history of cardiovascular disease. In a statistical analysis of the results which was designed to identify

independent determinants of endothelial dysfunction, only the presence of the metabolic syndrome emerged as significant with a huge odds ratio of almost 11. When the presence of the syndrome was removed from the analysis, neither gender nor age, CRP, interleukin-6, tumor necrosis factor or LDL were found to be an independent predictors. These results underscore the importance of the factors in the metabolic syndrome as being associated with the risk of the development and progression of atherosclerosis.

## FASTING GLUCOSE AND RISK OF CARDIOVASCULAR EVENTS

It has been pointed out several times in the literature that elevated fasting glucose is not a good predictor of insulin resistance. Nevertheless it is a component of the National Cholesterol Education Program definition of the syndrome. Thus a recent prospective study from Italy with a 15-year follow-up is of interest because it examined the ability of the metabolic syndrome to predict cardiovascular events, with and without fasting glucose. The participants were between 35 and 75 years of age roughly divided between men and women. It was found that the metabolic syndrome (as defined

above) was over twice as prevalent in women as in men. The syndrome increased the risk of cardiovascular events by about a factor of 2, a result similar to that reported above. When a survival analysis (freedom from cardiovascular events) was performed, the results did not significantly differ for those with the metabolic syndrome with impaired fasting glucose and those with the syndrome but normal fasting glucose. In other words, in this context, fasting glucose is irrelevant.<sup>7</sup>

## SPECIFIC TREATMENTS FOR THE METABOLIC SYNDROME

Scientists from the UK and Italy have recently examined the literature for guidance regarding evidence based treatments for the metabolic syndrome.<sup>8</sup> The options examined included diet, drugs and laparoscopic weight-reduction surgery (banded gastroplasty or gastric bypass). The studies were judged by the resolution of the syndrome, i.e. the fraction of participants who were no longer classified as having the metabolic syndrome after a follow-up of up to 5 years. The results were as follows

- **Diet.** Three randomized studies were examined. Two employed a Mediterranean type diet and one was part of the Diabetes Prevention Program. The later achieved a 20% resolution of the syndrome whereas the Mediterranean diets achieved 35% and 48% resolution. Follow-up was typically 2-3 years.
- **Drugs.** Studies examined involved glucose management drugs (metformin and rosiglitaxone). Three studies produced

resolutions of 33%, three of 30% and one of 5%. All were placebo controlled. The typical follow-up period was about 1 year.

- **Surgery.** The surgical approach to weight reduction turns out to be vastly superior to the above interventions. The studies involved mostly morbidly obese individuals and for the three studies included in the analysis, resolutions of 96%, 80% 97% and 93% were achieved with follow-ups running 6 months to 15 months.

The authors point out that while there is not yet an all-inclusive diet that targets all aspects of the metabolic syndrome, the evidence favors the Mediterranean diet since there is evidence that this diet pattern exerts beneficial effects on almost all components of the syndrome and other conditions associated with it including inflammation, insulin resistance and endothelial dysfunction.

## A HEALTHY LIFESTYLE. TURNING BACK THE CALENDAR BY 14 YEARS

What constitutes a healthy lifestyle continues to be the subject of studies and debate. While some may think of lifestyle in terms of exercise, smoking, etc, it is generally taken to include diet, the area of the greatest lack of consensus. A very large prospective study has just reported which attempts to simplify the lifestyle issues to just four which are equally weighted to provide a score of zero to four, with the highest score reflecting the healthiest behaviour

according to the view of the investigators.<sup>9</sup> The four factors were not smoking, being physically active, having moderate alcohol intake (1-14 drinks per week) and having a high intake of fruits and vegetables. For the latter, plasma vitamin C was used as a surrogate measure with a level of 50 mmol/L indicating fruit and vegetable intake of at least five servings per day. Relative risks for all-cause mortality for men and women (age 45-79

years) followed for 11 years were 1.39, 1.95, 2.52, and 4.04 for individuals having scores of three, two, one and zero compared to those with all four healthy behaviours. All of these relative risks were statistically significant with fairly narrow confidence limits. The authors calculate that having a score of 4 compared to zero is equivalent to being 14 years younger in chronological age. These results were consistent in subgroups stratified by gender, age, body mass index and social class and after excluding deaths that occurred within two years of enrolment. Thus smokers who were physically inactive, abstained from alcohol and did not include adequate amounts of fruits and vegetables in their diet had on average a 4-fold greater risk of mortality over 11 years than their opposites whose lifestyle was characterised by the healthiest behaviour score. The strongest benefit was seen in cardiovascular mortality. Non-cancer non-cardiovascular mortality was also strongly influenced by the healthy behaviour pattern. The intentional simplicity of this set of lifestyle factors seems very appealing. The authors comment that these results add to what is already “overwhelming evidence that behavioural factors such as diet, smoking and physical activity influence health. They cite two studies in particular which found huge impact.<sup>10,11</sup>

These studies bring to mind older landmark studies based on the Nurses’ Health Study which found that lifestyle and diet changes similar to those described above resulted in dramatic relative risk reductions for heart disease of 83% and type 2 diabetes of 91%.<sup>12,13</sup> In these two studies, the healthy diet pattern involved more than just lots of fruit and vegetables and included high cereal fiber and polyunsaturated fat, low *trans*-fat, low percentage of energy derived from refined carbohydrates, and avoiding being overweight or obese. Nevertheless, the basic philosophy is similar.

The official response to dietary research appears to be somewhat slow and inadequate. This is discussed in a recent commentary by Willett and Chiuve from Harvard. The title sets the stage for their views—“The 2005 Food Guide Pyramid: an opportunity lost?”<sup>14</sup> They provide evidence for why the new US Department of Agriculture pyramid does not take into account recent research and is inferior to the Healthy Eating Pyramid proposed in Willett’s book *Eat, Drink and Be Healthy. The Harvard Medical School Guide to Healthy Eating* (Simon and Schuster, 2001, 2005) which represents an attempt to optimize exercise and dietary, alcohol and supplement intake based on recent studies.

## CORONARY CALCIUM AS PREDICTOR OF CORONARY EVENTS

In the last decade, the assessment of the extent of coronary atherosclerosis using electron beam tomography (EBT) has become quite popular not only for screening but as a research tool. While coronary calcium predicts heart disease independently of traditional coronary risk factors, the influence of racial or ethnic background has not been investigated. In a study just reported in the *New England Journal of Medicine* Detrano et al<sup>15</sup> followed over 6700 men and women for almost 4 years for whom there was a baseline coronary artery calcium score (CACs). The subjects had no clinical cardiovascular disease at entry and the endpoints were any coronary event or a fatal or non-fatal heart attack. The cohort contained a diversity of ethnic or racial backgrounds including white, black, Hispanic, and Chinese. When individuals with zero coronary calcium were used as a reference point, those with scores between 101 and 300 had an increased risk of almost 8 fold and those with scores above 300, the risk increased to a factor of almost 10 times. For the major coronary events, the risks associated with calcium scores > 100 were increased by about a factor of 7. No

major differences among racial and ethnic groups were observed for the predictive value of the calcium score. It was also found that the calcium score provided predictive information beyond that provided by the standard risk factors. Unfortunately, the authors did not provide information on the correlation between calcium scores and individual traditional risk factors or the Framingham Risk Score. As discussed in the Cholesterol Research Review which appeared in recent issues of IHN, other studies have found poor correlation.

In an editorial accompanying this study, Weintraub and Diamond<sup>16</sup> discuss the value of the added predictive power of the calcium score and take the position that there is value only if patient outcomes improve. They comment that this could happen if the presence of coronary calcium prompted more aggressive blood pressure and blood lipid control. Aggressive blood lipid control for most involves statin drugs. Weintraub and Diamond have the conventional focus on serum cholesterol in spite of the absence of an association between either the Framingham Risk Score or cholesterol levels and

the extent of atherosclerosis as measured either at autopsy or by coronary calcium. Also, they appear to ignore the central role of inflammation and insulin resistance in the initiation and progression of atherosclerosis and thus ignore prime targets for intervention, especially in younger asymptomatic

individuals. The challenge here seems to be finding dietary and lifestyle interventions that will prevent, halt or reverse atherosclerosis. If this were to be successfully accomplished, then screening for coronary calcium would assume a major role in coronary heart disease prevention.

## **CORONARY HEART DISEASE. IS THE BATTLE BEING LOST?**

Over the past 20 years there has been a continuous decline in coronary heart disease mortality. It is thought that improvements in population risk factors and in medical treatments of patients with CHD have both contributed to this decline. However, when mortality is stratified by age, there are now signs of trouble ahead. A recent study provides data from the U.S. covering the period 1980-2002.<sup>17</sup> For the age group 35-44, for men the mortality rate now appears to be increasing and the decline stopped about 1998. For women the rate for this age group was both considerably lower than that for men and almost flat from 1980 to 2002, but there is also a suggestion of an increase starting in 2001. Similar

trends were found in a study of CHD mortality in England and Wales from 1984 to 2004, where for men aged 35-44, CHD mortality in 2002 increased for the first time in over two decades and the recent declines in CHD mortality for both men and women in the age range 45-54 appeared to be slowing.<sup>18</sup> In both papers, it is remarked that this may represent a sentinel event and the most likely explanation is the increase in obesity and diabetes. Since the impact of both diabetes and obesity on CHD mortality requires time to develop, the stage may well be set for a much more pronounced reversal in CHD incidence and mortality.

## **NEWS BRIEFS**

### **STATIN DRUGS AND THE BRAIN**

Anecdotal evidence is looked upon with profound disdain by mainstream medicine but in the absence of adequately powered studies, it is sometimes all that there is, especially as regards rare side effects of prescription drugs. Furthermore, anecdotal evidence is not welcomed in the peer review medical literature. Thus is not surprising to find a discussion of the effects of statins on memory and cognition in a different type of "journal," in this case *The Wall Street Journal* (WSJ) The WSJ article (February 12, 2008) leads off with a comment from Dr. Orli Etigen of New York Presbyterian Hospital who summarized his observations with "This drug makes women stupid." He cites a typical patient in her 40s who was unable to concentrate or recall words, but the symptoms vanished when she stopped taking Lipitor and returned when she resumed taking the drug. Dr. Etigen indicated that he has seen about two dozen such cases. These observations were echoed by Dr. Gayatri Deve who is quoted in the WSJ as saying she has seen at least six patients whose memory problems were traceable to statins in 12 years of practice. She feels the chronology involved helped established a causal relationship.

There is currently a study ongoing at the University of California at San Diego which is nearing completion. The lead researcher is quoted in the WSJ article as saying "We have some compelling cases." Again termination of the drug brings a very rapid return to normalcy.

The WSJ article fails to mention the book *Lipitor, Thief of Memory* by Duane Graveline, M.D. who is a former astronaut, aerospace medical research scientist, flight surgeon and family doctor. The book provides anecdotal evidence of the association between Lipitor and transient global amnesia. The author speaks from personal experience with this disorder.

Drug side effects, which occur only rarely, present a real challenge, especially if they concern cognitive matters. Cognitive changes are difficult to quantify and drug induced changes difficult to differentiate from changes caused by aging, vitamin B12 deficiency, etc. Studies that test new drugs for safety are not powered to detect rare side effects, and may not even aggressively look for changes in cognitive performance. Nevertheless, the changes can be devastating to the individuals concerned, and there needs to be a general awareness of this

problem, since when it is suspected, it is obviously important to test the hypothesis by stopping the drug temporarily.

### **STATINS AND TENDON PROBLEMS**

Evidence has been accumulating that tendon impairment may be another side effect associated with the use of statin drugs. The existing evidence has been reviewed by Marie et al from Rouen University Hospital in France.<sup>19</sup> They report that over 15 years from 1990 to 2005 there were 96 spontaneous reports of tendon complications reported to 31 French Pharmacovigilance Centers. Complications include tendonitis and tendon rupture. The median time to onset was somewhat less than a year but one case presented within 24 hours of taking the drug. Nearly one-third of those experiencing tendon complications had associated conditions that favored this side effect such as diabetes, hyperuricemia and participation in sports. The researchers attribute the tendon disorders to statin therapy because of temporal relationships, both with regard to onset and the resolution when cholesterol-lowering therapy was terminated and the recurrence when therapy was restarted. Current French recommendations include tendon disorders on the list of adverse effects of statins.

### **CENTRAL OBESITY AND DEMENTIA**

Central obesity, the so called beer belly in men, is considered to be a more significant risk factor for cardiovascular disease and diabetes than total body obesity such as would be measured by the body mass index (BMI). A study that employed data from Kaiser Permanente of Northern California has just reported which examined the association of abdominal diameter measured between 1964 and 1973 and the diagnosis of dementia on average 36 years later. Of the over 6500 participants, 15.9% were later diagnosed with dementia. When the lowest vs. the highest quintiles of the abdominal diameter were compared, there was almost a three-fold increase in the risk of dementia and this was only mildly attenuated by adding the BMI to the model. The authors comment that fifty percent of adults have central obesity and there is need for research to establish the mechanisms linking this to dementia.<sup>20</sup>

### **OLD BLOOD—BAD NEWS**

Normal practice with regard to the allowable storage period for red blood cells intended for transfusion is seven weeks, after which they are discarded. A study has just reported which compared the postoperative outcomes for individuals undergoing coronary bypass surgery depending on the age of the red cells used in transfusion. When storage for less than 14 days was compared with more than 14 days, a number of in-hospital endpoints showed a significant increase in incidence for those given older blood cells. Included were mortality, need for prolonged ventilatory support, kidney failure and septicaemia or sepsis. For example, mortality increased from 1.7% to 2.8% and septicaemia or sepsis from 2.8% to 4%. Also, the risk of mortality at one year was increased. In an accompanying editorial it was pointed out that to shorten the allowed storage time would greatly complicate blood-inventory management and result in restrictions on supply.<sup>21</sup> Thus individuals about to undergo this procedure should perhaps consider banking their own blood in case a red cell transfusion is needed.

### **WINE AND TYPE-2 DIABETES**

A recent study has examined the metabolic impact of one or two glasses of wine taken by diabetics with the evening meal or between dinner and bedtime. Serum glucose and insulin were monitored from before the meal until the next morning. The comparison was with white grape juice. The study also included chronic alcohol intake which involved one to two glasses per day for one month of red or white wine or abstaining from all alcoholic drinks for one month. The short-term studies of serum glucose and insulin were done in an inpatient setting with a controlled dinner and two glasses of white wine or white grape juice. No significant effects were observed in blood lipids, and the changes in blood glucose and insulin from dinner to the next morning were essentially identical with either grape juice or wine. However, in the long-term phase of the study it was found that fasting serum insulin was lower after one month of wine consumption as compared to abstinence. The authors point out that this is consistent with studies on non-diabetics where there reduced circulating insulin and increased insulin sensitivity was associated with wine intake. The increase in insulin sensitivity, according to the authors, might be a mechanism whereby alcohol exerts a cardioprotective effect in individuals with diabetes.<sup>22</sup>

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# The Prostate Monitor

## Editor: William R. Ware, PhD

*Reviews of recent studies from the peer-reviewed literature*

NUMBER 13

May 2008

2<sup>nd</sup> Year



*This issue will be devoted entirely to benign prostate hyperplasia (BPH), also known as an enlarged prostate. This disorder is widely prevalent in older men and eventually seriously impacts the quality of life due to what are called lower urinary tract symptoms (LUTS). These symptoms include frequent need to urinate, especially at night, severe and sometimes uncontrollable urge to urinate, low flow rate, failure to completely empty the bladder, and finally what is called acute urinary retention which obviously presents an immediate medical emergency, not only due to the associated severe pain, but also because of the risk of kidney damage. There are a number of non-pharmaceutical options that appear to slow the progression of BPH and also two classes of prescription drug, the alpha-blockers and the 5-alpha reductase inhibitors that are commonly used to*

*treat BPH.*

*This issue will be devoted entirely to BPH and the associated LUTS. BPH is a subject of an entire chapter in our book "The Prostate and Its Problems" which includes a discussion of non-pharmaceutical interventions which can impact the progression and severity of BPH. This is a health problem about which men need to be concerned given that most men by the age of 50-60 will find the associated LUTS at the very least bothersome.*

*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>

Benign prostatic hyperplasia involves the slow enlargement of the prostate which generally occurs with aging and which causes a number of urinary problems common to older men. The enlargement of the prostate is also associated with increased secretion of PSA and confuses the issue when PSA is used to assess the risk of prostate cancer. The use of PSA density, which takes this enlargement into account, represents an attempt to reduce the impact of this confounder. This subject is discussed in our book *The Prostate and Its Problems*.

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are highly prevalent conditions in older men. In the age group 60-69, it is estimated that 70% of men are afflicted with BPH, and the percentage increases with age. In the year 2000, BPH prompted over 4.4 million office visits, 117,000 emergency department visits, and 105,000 hospitalizations in the U.S. In general, the presently recognized risk factors for BPH and LUTS include obesity, elevated fasting glucose, elevated cholesterol and the metabolic syndrome. These will be recognized as also risk factors for cardiovascular disease.

### **HALTING PROGRESSION OF BENIGN PROSTATIC HYPERPLASIA WITH LYCOPENE**

Lycopene, a carotenoid mainly consumed from tomatoes, has been implicated in the prevention of prostate cancer, but clinical data regarding its impact on benign prostatic hyperplasia (BPH) has been lacking. Now a study has just reported which addresses this question with very interesting results.<sup>1</sup> Forty patients with BPH, no evidence of prostate cancer, and a PSA > 4 mg/mL were randomized to receive either 15 mg/day of lycopene or a placebo. At entry and after six months data from blood tests, a digital rectal exam, an ultrasound, and a questionnaire on urinary problems were collected. PSA was tracked at 1, 3, and 6 months and plasma lycopene determined. The 6-month lycopene supplementation decreased PSA levels by 0.74 mg/mL whereas there was no change in the placebo group. Both ultrasound measurements of prostate volume and the results of the digital rectal examination indicated that while progression of prostate enlargement occurred in the placebo group, there was no enlargement over this period in the lycopene group. A greater improvement in urinary function scores was also found for the lycopene group when compared to the placebo. The authors conclude that this daily dose of lycopene inhibited the progression of BPH. They speculate that the mechanism may involve inhibition of proliferation of benign prostate cells and, because lycopene is an antioxidant, the reduction of oxidative stress-mediated cell proliferation and remodelling of benign prostate tissue. They also take the position that lycopene does not selectively interfere with PSA levels and thus confuse the issue screening for prostate cancer, a problem with finasteride and dutasteride, the two drugs commonly used to treat BPH.

An examination of U.S. Department of Agriculture or industry data indicates that the major sources of lycopene are tomato juice (23 mg per cup), spaghetti sauce (20 mg per ½ cup) and watermelon (14 mg per 1/16 of a melon). By comparison one medium raw tomato provided 4.5 mg and ¼ cup of seafood cocktail sauce contained 7.3 mg. Supplemental lycopene is of course widely available in doses comparable to those used in the above study.

Hopefully this study will prompt larger studies which include dose dependence. Progression is normal in BPH and can eventually lead to so-called acute urinary retention which of course constitutes an emergency and frequently leads to surgical intervention. If lycopene were able to permanently halt this progression at a point where the urinary symptoms were mild or at least tolerable, this would represent huge progress, including the prevention of acute episodes, in this very prevalent disorder.

### **DIET AND RISK OF BPH**

A large, U.S. multi-center follow-up study of dietary factors associated with the incidence of BPH has just reported.<sup>2</sup> Over 4700 men (age 54 or older) initially free of BPH were followed for 7 years. The incidence of BPH was defined as the need for medical or surgical treatment or repeated elevations in the International Prostate Symptom Score, a measure of LUTS. During the study period 876 cases of BPH were documented, which allowed the calculation of risk based on data collected from a food frequency questionnaire which evaluated diet, alcohol and supplement use. When the highest vs. the lowest quintiles of intake were compared, BPH risk was positively associated with total fat and polyunsaturated fat intake and decreased by high protein intake. The risk was significantly lower in high consumers of alcoholic beverages (0 vs. ≥ 2 per day) and vegetables. Red meat

was found to increase risk. As regards supplements, there was weak evidence for associations with lycopene, zinc (dietary) and supplemental vitamin D. For vitamin D, the top quintile of total intake from diet and supplements was about 650 IU and thus the range of intake was somewhat below what is considered desirable for disease prevention. The upper quintile for lycopene from diet was about 12.8 mg/day. This is below the level used in the above study. In the diet study incidence, not progression was the issue. However, the figure is interesting since it implies that for most men in this study, the estimated lycopene intake was considerably below that used in the progression study, and suggests that unless attention is directed specifically at increasing dietary intake, men should consider supplementation.

The authors comment that their results are more or less consistent with earlier studies. In fact, a number of studies have found regular alcohol consumption was associated with decreased risk. They suggest this is due to the effects of alcohol on the production and metabolism of testosterone. There was no association with either tea or coffee. Also, they did not confirm the results of an earlier study which showed an increase risk associated with the long chain omega-3 fatty acids (EPA and DHA). The finding of a decrease in risk with high protein intake, according to the authors, is novel and requires replication. Also, this study did not support an association of antioxidant nutrients with BPH risk. Since there was no correlation between supplemental zinc and the risk of BPH, they suggest that the weak correlation with dietary zinc may be due to confounding by protein intake.

### **PHYSICAL ACTIVITY, BPH AND LOWER URINARY TRACT SYMPTOMS**

A recent study from the University of California at San Diego reports on an investigation concerning physical activity and BPH and LUTS.<sup>3</sup> Part of the motivation for the study came from the fact that these disorders share risk factors with cardiovascular disease (CVD) and physical activity has a significant impact on the risk of CVD. This was a study based on earlier studies and examined pooled results. Eleven studies involving over 43,000 men met the inclusion criteria and eight were eligible for pooled analysis. Physical activity was stratified into light, moderate and vigorous categories with a sedentary category used as the reference. Light physical activity failed to exhibit a statistically significant benefit, but moderate and vigorous activity yielded approximately a 25% risk reduction which was statistically significant.

The authors point out that their results challenge the traditional view that BPH and LUTS are relatively immutable consequences of aging—driven by a combination of genetic predisposition, androgen and estrogens, and that this view may need to be expanded to include the connection with factors also associated with cardiovascular health. The metabolic syndrome for example is associated with systemic inflammation, and the authors comment that inflammation potentially drives BPH. Also, BPH/LUTS often occurs in association with erectile dysfunction which in turn is strongly associated with cardiovascular disease (atherosclerosis), and this suggests a common etiology. Also, increased physical activity has been associated with a lower risk of erectile dysfunction.

### **PROSTATITIS AND BPH**

In outpatient urology clinics, prostatitis is the most common presenting diagnosis for men less than 50 years of age and its prevalence is estimated to range between 2 and 16%, depending on the population studied and the definitions used. The nature, diagnosis, prevention and treatment of prostatitis are the subject of the first chapter in our book.

The symptoms of prostatitis and BPH overlap and thus it is debated whether one syndrome precedes the other, whether the two syndromes may coexist, and whether prostatitis might serve as a marker or risk factor for the development of BPH-associated events. A recent study has addressed one of these issues, i.e. might prostatitis precede the development of BPH and thus be a marker or risk factor for later urologic problems. Medical records for 2447 men residing in Olmsted County, Minnesota were reviewed for physician diagnosed prostatitis and the subsequent diagnosis of BPH. Patients who had been diagnosed with prostatitis had a 2.4-fold greater risk of later being diagnosed with an enlarged prostate or BPH as compared to men without the prior prostatitis diagnosis. Also, there was an increase of 70% in the odds of requiring later treatment for BPH. But the odds of having an acute urinary retention episode did not reach statistical significance. However, the results failed to clarify the question of whether or not prostatitis was a true risk factor or just an early marker for BPH.<sup>4</sup>

These results suggest that the prevention of prostatitis should be included in BPH prevention strategy. The reader is referred to our book where there is a section on the prevention of this disease.

## COMBINATION THERAPY FOR BPH/LUTS

Both alpha-blockers and 5-alpha reductase inhibitors are widely used for the treatment of the symptoms of BPH/LUTS. It is also not uncommon for so-called combined therapy to be prescribed which makes use both classes of drug. An industry supported study of combination therapy with tamsulosin (Flomax) and dutasteride (Avodart) has just reported.<sup>5</sup> Tamsulosin is a so-called uro-specific alpha-blocker which does not have the same impact on blood pressure associated with older alpha-blockers and the dose does not have to be slowly increased to avoid adverse blood pressure events. Avodart belongs to the same general class of drug as Proscar and recently has been heavily promoted on prime-time TV. The study in question compared the results with each drug separately as well as with the combination of both drugs. The trial was randomized and double-blind. Men 50 years older with a clinical diagnosis of BPH who had a PSA  $\geq 1.5$  (mean approximately 4), a prostate volume  $\geq 30$  cc (mean approximately 55 cc) were randomized to 0.5 mg/day of Avodart, 0.4 mg/day of Flomax, or both for 4 years. The primary endpoint was the change in the International Prostate Symptom Score from baseline. Combination therapy resulted in significantly greater improvements in symptoms vs. Avodart after 3 months and Flomax after 9 months. There was a significantly greater increase in peak urinary flow for combination therapy vs. the individual drugs after 6 months. Combination therapy was associated with greater adverse side effects than either drug alone, but most did not result in cessation of therapy. As expected, PSA declined to approximately half the baseline value when Avodart was used as all or part of the therapy.

Combination therapy may appeal to some men who have decided to go the pharmaceutical route since the 5-alpha reductase inhibitor results in a decrease in prostate volume as well as an improvement in LUTS symptoms. The issue of a decline in the risk of prostate cancer, either localized or advanced or both, remains open at this point. But if studies find a decrease in risk for both, this would provide added incentive. For the competitive drug Proscar, there was a decline in prostate cancer risk for localized but an increase for advanced disease, although there has been much discussion regarding the possibility that this latter result was an artifact.

## INFLAMMATION OF THE PROSTATE—RELATED TO BPH, CANCER OR BOTH?

The role of inflammation in both prostate cancer and BPH has been the subject of some debate. One of the problems with issue is that an unknown proportion of prostatic inflammation is not associated with any clinical sign or symptom. This is frequently referred to as Category IV prostatitis (asymptomatic inflammatory prostatitis). Also, there is the problem of an appropriate control for comparison. A recent study has attempted to resolve some of these problems by examining prostate specimens obtained at autopsy with those devoid of either BPH or prostate cancer acting as controls.<sup>6</sup> Laboratory methods were used to assess the presence of inflammation in tissue samples obtained from areas associated with prostate cancer or BPH. The researchers were also able to differentiate chronic prostate inflammation from acute inflammation. It was found that the chronic inflammation was a common finding in all autopsied prostates and appeared to be directly associated with the presence of BPH but not cancer. That is, chronic inflammation was significantly more prevalent in glands with BPH compared with glands with no BPH or with cancer. The prevalence of chronic inflammation was not associated with prostate cancer. Acute inflammation was not significantly associated with either prostate cancer or BPH.

These results are consistent and add to the study reported above regarding the association between prostatitis and BPH.

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The Prostate Monitor is published 10 times a year by  
International Health News, 1320 Point Street, Victoria, BC, Canada, V8S 1A5  
Editor: William R. Ware, PhD  
e-mail: [editor@yourhealthbase.com](mailto:editor@yourhealthbase.com)  
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**Editor: William R. Ware, PhD**  
INTERNATIONAL HEALTH NEWS is published 10 times a year by  
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5  
E-mail: [editor@yourhealthbase.com](mailto:editor@yourhealthbase.com) World Wide Web: <http://www.yourhealthbase.com>

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