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INSIDE

Do Diets that are Named After People Work Better?

ABSTRACT & COMMENTARY

Synopsis: *Adherence to any diet was the best predictor of weight loss, which predicted degree of improvement in cardiac risk markers.*

Source: Dansinger ML, et al. *JAMA*. 2005;293:43-53.

THIS WAS A RANDOMIZED, SINGLE-CENTER, YEAR-LONG PROSPECTIVE study. Forty participants (160 total) were randomized to each of the following diets: Atkins, the Zone, Weight Watchers, or Ornish. Participants were recruited by newspaper and television ads. To be included, participants had to be overweight or obese, and to have one of the following: elevated fasting glucose, elevated cholesterol, elevated low-density lipoprotein (LDL), elevated triglycerides, hypertension, reduced high density lipoprotein (HDL), or current treatment of hypertension, diabetes, or dyslipidemia. They were not compensated for participating. For the first 2 months, a dietician and physician met with small groups of participants for 1 hour on 4 occasions, and gave diet-specific teaching and advice. All participants, regardless of the diet to which they were assigned, received standard information about exercise, external support, and supplemental vitamins. After the first 2 months, participants no longer had to go to meetings, but were asked to follow their assigned diet according to their own interest level. Outcome measures were assessed at 2, 6 and 12 months, and included weight, cardiac risk factors, exercise, and dietary adherence.

The participants were representative of the US population, and were matched between diet groups. Overall, their mean age was 49 years, and mean Body Mass Index (BMI) at entry was 35 kg/m^2. 51% were women, 75% were white, and 13% were smokers. Attrition rate at 1 year was 50% for Ornish, 48% for Atkins, 35% for Zone and for Weight Watchers, and 42% overall. There was no statistically significant difference in weight loss in adherent participants at 1 year, with about 25% of participants overall sustaining a 1-year weight loss of more than 5% of initial body weight. The mean weight loss in kilograms (and pounds) for each diet at 12 months for those who did not drop out was 6.6 kg (14.5 lbs) for

VOLUME 27 • NUMBER 4 • FEBRUARY 29, 2005 • PAGES 25-32

Ornish, 4.9 kg (10.8 lbs) for Zone, 4.6 kg (10.1 lbs) for Weight Watchers, and 3.9 kg (8.6 lbs) for Atkins. There was a very strong correlation between self-reported dietary adherence and weight loss. For each group, dietary adherence decreased progressively over time. The most common reasons cited for discontinuation were that the assigned diet was too hard to follow or was not yielding enough weight loss. No adverse events were documented in any participants. All diets resulted in statistically significant but modest improvements in cardiac risk factors, with the exceptions that the Atkins diet did not reduce LDL levels, the Ornish diet did not improve HDL levels, and no diet improved triglycerides, blood pressure, or fasting glucose. The degree of improvement in cardiac risk factors correlated with the degree of weight loss. Dansinger and colleagues comment that "no single diet produced satisfactory adherence rates . . . the higher discontinuation rates for the Atkins and Ornish diet groups suggest many individuals found these diets to be too extreme . . . we suspect that adherence rates and clinical improvements would have been better if participants had been able to freely select from the 4 diet options."

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

What a shocker! People don't stay on diets! Who knew? This paper is a desperately needed attempt to compare diets in a real life situation. Alas, it confirms what we already knew: it's the calories, stupid. People who stick with a diet, any diet, lose weight, and people who don't, don't. With that shocking revelation, let's look at a couple of findings that Dansinger et al don't emphasize much: the attrition rate at 1 year (which predicted weight loss) ranged from 35% to 50%. While this is not statistically significant ($P = 0.08$) in this relatively small sample, it is likely to be significant in the obese population at large. Two of the diets in this study resulted in roughly a 50/50 chance the patient would drop out, and 2 resulted in only a 1 in 3 chance that the patient would drop out. So, while I agree with Dansinger et al that participants likely found the Atkins and Ornish diets too extreme, I do not agree that outcomes would have been better if the participants had a choice of diets. Participants already do have a choice of diets. Most obese or overweight folks have been through several different diets. And they drop out, not only because dieting is hard and weight loss is slow, but also because there is a confusing array of diets and choices, and the main message (it's the calories, stupid) gets lost in the hype and the search for the quick fix. My take on this, given that the primary reasons for attrition were that the diets were too hard or weren't producing fast enough weight loss, is that we have given an inconsistent and unrealistic message. Weight loss isn't easy, it isn't fast, and there is not magic diet (or bullet). Losing 10 pounds in a year doesn't sound like much to folks who have a 100 or more pounds to lose, but the odds are that losing 10 pounds in a year is a huge improvement over what happens if they don't work at it.

Lest the reason we eat get lost in the shuffle, Eckel points out in the accompanying editorial,[1] that attention to nutrition is also important. Another shocker! He reminds us of the recent joint statement of The American Cancer Society, American Heart Association, and American Diabetes Association,[2] which focuses on fruits, veg-

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etables, fish, grain and all that boring stuff. Dr. Eckel urges rational eating, for nutrition, which he dubs the "Low Fad" approach.

I think the take home messages are that it is the reduction in calories, not the diet itself that matters, that adherence is a critical factor, that extreme diets are more difficult to adhere to, and that weight loss is hard! I have started giving a very consistent message to my patients about weight loss. Because I think patients need support, because it has long term data on huge numbers of patients and works better than self-help,[3] because it is readily accessible in a variety of formats, and because lifetime memberships are available for this lifelong problem, I now recommend Weight Watchers to everyone. And I try to remember to remind them that we eat for nutrition, that weight loss is not easy, and that anyone can lose weight; the hard part is keeping it off. ■

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Is Obesity a Risk Factor for Atrial Fibrillation?

ABSTRACT & COMMENTARY

Synopsis: *Obesity is an important, potentially modifiable risk factor for AF. The excess risk of AF associated with obesity appears to be mediated by left atrial dilatation. These prospective data raise the possibility that interventions to promote normal weight may reduce the population burden of AF.*

Source: Wang JT, et al. *JAMA*. 2004;292:2471-2477.

Atrial fibrillation (AF) is the most common cardiac dysrhythmia currently afflicting 2½ million Americans and its frequency is expected to increase several-fold in the next one or two decades.[1] Previously reported studies have demonstrated that diabetes, hypertension, advanced age, and the presence of cardiovascular disease increase the risk of developing AF[2-5] and, most recently, obstructive sleep apnea which occurs in about 40% of obese individuals has also been found to be strongly associated with AF.[9] Despite the fact that obesity frequently occurs in association with most of these conditions, the data from prior studies have not been clear as to whether or not obesity is a specific risk factor for AF in and of itself.[2-5]

Wang and associates used the data from the prospective, community-based Framingham Heart Study and the Framingham Offspring Study[6,7] to collect information on 5282 participants whose mean age was 57 years (55% women) without baseline AF. Subjects were categorized as normal if their body mass index (BMI) was less than 25, overweight if it was 25-30, and obese if it was greater than 30. During the mean follow-up of 13.7 years, 526 participants (234 women) developed AF. After adjusting for cardiovascular risk factors and interim myocardial infarction or heart failure, a 4% increase in AF risk for a one unit increase in BMI was observed both in men and women. However, after adjustment for echocardiographic left atrial diameter in addition to the clinical risk factors, BMI was no longer associated with an increase in AF risk. Therefore, the excess risk of AF associated with obesity appears to be mediated by left atrial dilatation.

■ COMMENT BY HAROLD L. KARPMAN, MD

Obesity has reached epidemic proportions in the United States in that nearly 65% of the population are overweight and 31% are classified as obese.[8] Similarly, as indicated above, AF is also reaching epidemic proportions. Wang et al have now clearly demonstrated that obesity was correlated with a 50% increase risk of developing AF irrespective of sex. Equally important, they demonstrated that after adjusting for left atrial diameter, obesity was no longer associated with increased risk for the development of AF. Left atrial remodeling is an established mechanistically important factor in the pathogenesis of AF whether by increasing left atrial size or by other mechanisms such as allowing for the occurrence of a critical number of reentrant wavelets, by left atrial stretch or by triggering pulmonary vein foci.[10,11]

Although the Framingham data are observational, it clearly raises the strong possibility that weight reduction may decrease the risk of developing AF. Although the increased risk for the development of AF in patients with an increased BMI is modest, the public health implications are quite significant since AF is responsible for a 3-5-fold increase risk of stroke and a 2-fold increase risk of mortality.[1] Older age is clearly the most important risk factor for the development of AF for a variety of electrophysiological reasons. Of course, one cannot change their age; however, it would now appear clear that control of diabetes and hypertension as well as lifestyle changes aimed at weight reduction in obese individuals may prove to be critically important in preventing the onset of AF, and thereby reducing the mor-

bidity and mortality associated with that arrhythmia. Finally, it is important to note that additional prospective studies are needed to understand the influence of excessive weight on the cardiac remodeling process and to document the effects of weight loss on the risk of developing new onset AF. ■

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Accuracy of Screening for Fecal Occult Blood on a Single Stool Sample Obtained by Digital Rectal Examination

ABSTRACT & COMMENTARY

Synopsis: *A single fecal occult blood test from a digital rectal exam specimen does not provide adequate screening for colorectal neoplasia and cannot replace standard at-home 6-sample fecal occult blood testing.*

Source: Collins JF, et al. *Ann Intern Med*. 2005;142:2:81-85.

MANY PHYSICIANS ROUTINELY SCREEN FOR advanced colonic neoplasia by occult blood testing of stool obtained from a digital rectal exam. Several limited studies have suggested that fecal occult blood testing (FOBT) on specimens obtained at rectal exam could produce similar positive predictive values for colon pathology. Collins and colleagues have performed the first large-scale trial to elucidate the sensitivity and specificity of digital FOBT vs standard 6-sample FOBT by performing colonoscopy on all patients with both positive and negative FOBT results. Also, 3121 asymptomatic patients in 13 VA medical centers participated out of 17,732 persons screened for study inclusion. As expected, virtually all participants were men with an average age of 63 years (50-75 years of age). All had digital rectal exams including FOBT on stool specimens so obtained, and all performed at-home collection of 2 smears from each of 3 spontaneously passed stools. Although patients were told to restrict red meat, vitamin C, and aspirin, compliance was not monitored. Because some patients did not collect their at-home FOBT specimens and because stool was not always available in the rectal vault for testing of the digitally obtained specimen, 2,665 patients were evaluable. Most participants were Caucasian; 1,218 patients (45.7%) had no polypoid lesions of any kind. In 438 patients, hyperplastic or other non-neoplastic lesions were identified. Of 1,656 patients without adenomas, digital FOBT was positive in 41 (specificity 97.5%; CI, 96.8-98.3%). At least one window of the Hemoccult II™ tests was positive in 101 of these patients (specificity 93.9%; CI, 92.7-95.1%). In 725 patients, 1 or more tubular adenomas less than 10mm in size were identified. Digital FOBT was positive in 4% and the 6-sample test was positive in 6.3%. 284 patients were found to have advanced neoplasia (10.7% of the whole population included). Results of digital FOBT were positive in 14 of these patients vs 68 testing positive with the 6-sample FOBT. The sensitivity of the 6-sample test for advanced neoplasia was 23.9% vs only 4.9% for digital FOBT. Specificity for advanced neoplasia was 93.8% vs 97.1%. There was no evidence that adding the digital FOBT to the 6-sample home technique would identify significant additional pathology. Collins et al admitted that a positive digital FOBT is significant and that it should mandate colonoscopic evaluation. Importantly, their major conclusion is that digital FOBT is not adequate as screening for advanced colon neoplasia.

■ COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

As this paper points out, there are limitations to its findings. First, since virtually no women were included in this VA population, results are not necessarily generalizable to women. Second, this study used rehydration of the Hemoccult II slides, a technique that may increase sensitivity while decreasing specificity (no longer recommended for FOBT). It is also possible (even likely) that some neoplastic lesions were missed although these were highly experienced colonoscopists. In a somewhat cute editorial in the same issue of *Annals of Internal Medicine*, physicians are chided for their ignorance regarding appropriate colorectal cancer screening, and

they are urged to put their Hemoccult slides in a locked drawer, labeled: For Emergency Use Only. However, I am not certain that the dismissal of digital FOBT is altogether reasonable. Many of our patients refuse to prepare at home slides for FOBT, and tests that are not performed will certainly do no good. Also, it is hard to be impressed with the highly unsatisfactory results of our *gold standard* test of 6-sample at-home FOBT. After all, even done properly, this test misses more than three quarters of advanced colon neoplasia. For my money, we need better tests. In a recent article, fecal DNA testing was discussed. Although not yet ready for widespread adoption, this seems to me to be a more promising direction than any approach that depends on occult blood detection. After all, many advanced neoplastic lesions don't bleed at all. However, all of them must be shedding cells. We need to identify the signature (genetic or otherwise) of colon neoplasia as a means of directing colonoscopic intervention. For now, I don't agree that we should abandon digital rectal exams including FOBT. An inadequate test is better than none at all. On the other hand, I agree with Collins et al that we should not pretend that a negative digital FOBT rules out significant colon neoplasia—as it certainly does not. We should redouble our efforts to achieve universal adherence to at-home FOBT in the pertinent patient populations, and we should try even harder to come up with a test that really works. ■

Niacin Plus Statins For Low HDL

ABSTRACT & COMMENTARY

Synopsis: *The addition of niacin to patients with known CAD on statins raised HDL cholesterol and reduced atherosclerosis progression.*

Source: Taylor AJ, et al. *Circulation*. 2004;110: 3512-3517.

Although good at lowering LDL cholesterol, statins do not raise HDL enough in many patients. Niacin is the most effective therapy for low HDL, but little information exists about combination niacin and statin therapy on cardiovascular outcomes. Thus, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study was conducted at Walter Reed Army Medical Center to evaluate the effect of adding niacin to statins on carotid intima-media thickness (CMT) in patients with known coronary artery disease (CAD). This was a double-blind, randomized, placebo-controlled study in 167 patients with CAD documented by myocardial infarction or coronary revascularization. Patients on statins with LDL < 130 and HDL < 45, and no known contraindication to niacin, were randomized to placebo or extended-release niacin starting at 500 mg for 30 days, then 1000 mg for 11 months. Only 4 patients had their statin dose changed during the study. The primary end point of CMT change at 1 year was increased in the placebo group by 0.044 mm (P < .001) and was unchanged in the niacin group, 0.014; P = 0.23. LDL was 89 at baseline and was unchanged by niacin therapy. HDL averaged 39 in the niacin group at baseline and increased to 47 (P < .001); there were no changes in the placebo group. Triglycerides also decreased in the niacin group (164 to 134; P < .01), but fasting glucose increased (107 to 123; P = 0.017). CRP measures were unchanged by niacin. Patients without insulin resistance (diabetes or metabolic syndrome) on niacin had the lowest progression rate of CMT. Cardiovascular events occurred in 3 niacin patients and in 7 placebo patients (P = NS). Study drug adherence was > 90%, and not different between placebo and niacin. No patient had liver tests > 3 times the upper normal limit, and none had myositis. The majority of patients on niacin noted skin flushing. Taylor et al concluded that the addition of niacin to patients with known CAD on statins raised HDL cholesterol and reduced atherosclerosis progression.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Although it is well-known that niacin raises HDL levels, the value of this effect, in addition to statins and its tolerability, has been poorly defined. The coronary drug project evaluated niacin monotherapy and showed a reduction in nonfatal myocardial infarction and 15-year mortality, but other studies employing niacin included it with other agents, making it difficult to tease out the effects of niacin alone. This is the first study of moderate-dose niacin added to statins in a systematic, controlled fashion. The study was not powered for clinical outcomes, but rather used CMT as a surrogate. Despite an average duration of statin therapy of about 5 years and average LDL levels of 85 to 90, the placebo group showed progression in CMT. There are several explanations for this: The low HDLs, high triglycerides (average > 150), or failure to drive the

LDL below 80 in all the statin patients. Niacin addressed the first 2 issues and showed a lack of progression, thus, indirectly supporting the value of raising HDL and lowering triglycerides. These results are also concordant with the results of a small study of the effect on vessel walls of infusing man-made HDL.

Niacin seemed to be well-tolerated at this dose. Although most patients had skin flushing, few discontinued therapy. Also, liver tests were not alarmingly elevated (> 3 times the upper limit), but the report did not give the actual liver function test data. So elevations < 3 times the upper limit probably were observed. No muscle problems were reported. Thus, this long-acting niacin preparation given at bedtime in moderate doses seems like a reasonable approach to those with low HDL on adequate statin therapy.

Since most of the subjects were on simvastatin, we do not know if more potent statins with greater LDL-lowering would have worked just as well. Also, the role of fibrates, which also increase HDL and reduce triglycerides, either alone or in combination with statins, is unclear. However, the fibrate statin combination probably has more potential for adverse effects. Finally, the suggestion that patients with diabetes or the metabolic syndrome do not do as well on the statin and niacin combination requires more study. ■

Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology; University of California, San Francisco.

Suicidal Ideation in Patients with Irritable Bowel Syndrome

ABSTRACT & COMMENTARY

Synopsis: *Although irritable bowel syndrome (IBS) is mostly viewed as a nuisance disease without serious consequences, a surprisingly large number of IBS patients may suffer severe depression, hopelessness, and consequential suicidal ideation.*

Source: Miller LV, et al. *Clinical Gastroenterology and Hepatology*. 2005;2:12:1064-1068.

Without any doubt, IBS is the most common gastrointestinal condition seen by primary care physicians and gastroenterologists. Patients with this condition often describe symptoms as severe and disabling. Quality of life in IBS patients can be as bad as diabetes or renal failure. Medical therapy for IBS has been mostly ineffective. Miller and colleagues, concerned by suicides by IBS patients in their own tertiary population, decided to analyze pertinent parameters in tertiary care IBS patients, secondary care IBS patients, primary care IBS patients, and in patients with active inflammatory bowel disease (IBD). In this study, 100 patients were anonymously surveyed in each of these groups; 67-79% of surveys were returned. Questions involved demographic data, severity of illness symptoms, anxiety, and depression. Patients with IBD and primary care IBS patients were younger than the secondary and tertiary IBS groups. Disease history was longer in tertiary IBS patients and in IBD patients. IBS was associated with more anxiety and depression. Primary care IBS patients and IBD patients rated symptoms as less severe than tertiary IBS patients. Tertiary IBS patients were most likely to be unemployed. Suicide related specifically to disease symptoms had been contemplated by 38% of tertiary IBS patients vs 4% of primary care IBS patients and 16% of IBS patients in secondary IBS care settings. IBD patients described disease-related suicidal ideation in 15% of cases. For demographic reasons, it appears that 5 times more IBS patients are suicidal vs IBD patients. Overall, Miller et al point out a striking prevalence of suicidal ideation in severe IBS. Although there is some correlation with depression and suicidal ideation in these patients, these authors believe that suicidal ideation may be most closely linked to the hopelessness of a disease from which recovery or respite seem impossible. Miller et al believe that suicidal ideation is more a marker for distress than an invariable harbinger of actual suicide (although 5 tertiary IBS patients had actually attempted suicide vs only one other patient in the study—an IBD sufferer). These English gastroenterologists suggest that direct personalized supportive therapy may be our best currently available approach to these unhappy patients.

■ COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This paper serves as a reminder that *benign* disease can be perceived as overwhelmingly severe by our patients. Gastroenterologists in tertiary care settings may be the most likely to see the worst of the worst of these patients. However, even in primary care, awareness of the distress that may be felt by IBS patients remains important. The regular use of simple self-administered tests for anxiety and depression in our

patients may be appropriate. This has always been my practice and I have found it to be extremely helpful. Clearly, there is a place for the judicious use of anxiolytic and antidepressant medications, but I agree with the authors that supportive caregivers may ultimately do more good than any of our current drugs. A great deal remains to be learned about IBS and its treatment, including the management of potentially serious emotional disturbances in these patients. ■

Pharmacology Update

Oxycodone and Ibuprofen Tablets (Combunox™)

By William T. Elliott, MD, FACP and James Chan, PhD, PharmD

A FIXED COMBINATION OF THE NARCOTIC ANALGESIC oxycodone and the nonsteroidal anti-inflammatory agent ibuprofen has been approved for the short-term treatment of acute moderate-to-severe pain. This first time combination of these 2 agents is marketed by Forest Laboratories as Combunox™.

Indications

Oxycodone/ibuprofen is indicated for the short-term (no more than 7 days) management of acute, moderate-to-severe pain.[1]

Dosage

The recommended dose is one tablet, not exceeding 4 tablets in 24 hours.

Oxycodone/ibuprofen is supplied as tablets containing 5 mg of oxycodone and 400 mg of ibuprofen.

Potential Advantages

The combination potentially provides additive analgesic effect of 2 different analgesics without substantially increasing adverse events.

Potential Disadvantages

The addition of 5 mg of oxycodone to ibuprofen 400 mg produced similar analgesia to ibuprofen 400 mg in an oral surgery pain model.[2] Oxycodone/ibuprofen is approved for acute use only, no more than 7 days. No multiple dose studies have been conducted with this combination.[1] It is a schedule CII controlled substance requiring the Schedule II security prescription form.

Comments

Oxycodone/ibuprofen was studied in 3 single-dose clinical trials, 2 in patients following dental surgery (n = 949) and the third following abdominal/pelvic surgery (n = 456). Patients were randomized to placebo, oxycodone, ibuprofen, or the combination. Magnitude of pain relief and reduction in pain intensity were assessed over 6 hours. Oxycodone/ibuprofen was reported to be more efficacious than placebo and each individual component.[1] However, in a published study using an oral surgery pain model (removal of 2 or 4 molars) (n = 118) the addition of oxycodone 5 mg to ibuprofen showed no statistical difference in analgesia as assessed by the time course of pain intensity using a visual analog scale or pain relief.[2] The addition of 10 mg of oxycodone produced significant analgesia over ibuprofen or ibuprofen plus 5 mg oxycodone but also produced greater frequency of adverse effects. The analgesic advantage was detected only over the first 2 hours. The wholesale cost of oxycodone/ibuprofen is $1.20 per tablet.

Clinical Implications

It is not clear if this new fixed combination offers any clinical advantages over available analgesic combinations as comparative multiple dosing comparisons are not available. ■

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CME Questions

7. In a prospective comparison of Weight Watchers, the Zone, Ornish, and Atkins diets, adherence and participation rates at 1 year:

a. were remarkably similar among diets.
b. had no effect on cardiac risk factors.
c. resulted primarily from side effects of the diets.
d. correlated strongly with weight loss.
5. robustly predicted blood pressure change.

8. In this study from the United Kingdom, suicidal ideation was seen in what proportion of severe IBS patients in tertiary care settings?

a. 8%
b. 18%
c. 21%
d. 38%
e. 78%

Answers: 7 (d); 8 (d)

By Louis Kuritzky, MD

Sildenafil Citrate for Erectile Dysfunction in Men Receiving Multiple Antihypertensive Agents

ERECTILE DYSFUNCTION (ED) IS commonplace in men at middle-age and beyond, the same era when hypertension (HTN) incidence begins to rise steeply. Since ED is widely recognized as a vasculopathy, in large part related to endothelial dysfunction, HTN can contribute to the burden of ED. Additionally, antihypertensive medications can lead to ED.

Sildenafil can produce dramatic, potentially disastrous blood pressure reductions if concomitantly administered with organic nitrates (eg, nitroglycerin), and is thusly contra-indicated. Little studied is the efficacy and safety of sildenafil in men already on multiple antihypertensive agents.

Pickering and colleagues studied middle-aged men with ED (n = 562), all of whom were taking 2 or more antihypertensives. Men were randomized to sildenafil (titrated to most efficacious, best tolerated dose) or placebo, and monitored for medication efficacy as well as adverse events.

Sildenafil provided efficacy in restoring erectile function similar to that seen in prior trials including non-hypertensive patients. It was also well tolerated, and sildenafil-related hypotension was not identified. These data are encouraging that sildenafil may be used safely and efficaciously in men already receiving multi-drug regimens for HTN. ■

Pickering TG, et al. Am J Hypertens. 2004;17:1135-1142.

Risk of Fracture after Androgen Deprivation for Prostate Cancer

IN THE POPULATION OF MEN WITH advanced prostate cancer (PCA) as a whole, androgen deprivation, through medical or surgical orchiectomy, produces benefits in morbidity and mortality. In 2 distinct PCA populations—men with localized disease, and men with post-prostatectomy PSA elevations—gonadotropin-releasing hormone agonists (GNRH) are finding increased use, despite lack of proof for survival advantage. Because androgen deprivation results in rapid bone loss, an increased risk of fracture would be anticipated to result. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and Medicare provided the information from which 50,613 men with prostate cancer could be studied.

Between 1992 and 1997, the relative risk of any fracture for men who had received nine or more doses of 9 was increased approximately 1.5 fold. The relative risk for fracture requiring hospitalization was even greater. Indeed, men who received orchiectomy or greater than 9 doses of GNRH in the year after diagnosis had a lower fracture-free survival rate, compared with those who did not receive androgen deprivation. Noting these risks, Shahinian and colleagues suggest caution, at least in the distinct populations mentioned above, in use of androgen deprivation until benefits of treatment are more clearly delineated. ■

Shahinian VB, et al. N Engl J Med. 2005;352:154-164.

Chronic Stress Accelerates Ultraviolet-Induced Cutaneous Carcinogenesis

LONG-TERM CONSEQUENCES OF stress in human beings are difficult to measure, but it is believed that excessive emotional stress contributes to important adverse health outcomes such as myocardial infarction. Whether stress impacts cancer is little understood. To elucidate this issue, Parker and colleagues studied carcinogenesis in animals.

Mice were exposed to the stressor of being placed in a compartment (without opportunity for escape) for 60 minutes daily containing odor from fox urine, one of their natural predators. After 2 weeks of daily stress, the frequency was reduced to thrice weekly for 30 weeks. During the study period, animals were irradiated with UV light known to induce skin lesions.

Animals exposed to stress began to manifest neoplasm dramatically earlier than control animals (8 weeks vs 21 weeks), and with greater frequency (5 fold-increase in stress-subjected animals). Stressed animals in which tumors developed survived less well compared to controls (who also developed tumors). Although animal studies do not directly translate into human agenda, these data support the conceptual framework for a deleterious impact of stress upon carcinogenesis, as well as survival from established carcinoma. ■

Parker J, et al. J Am Acad Dermatol. 2004;51:919-922.

In Future Issues: High-Dose Vitamin E Increases All-Cause Mortality