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Effect (or Noneffect) of Oral Androstenedione on Serum Testosterone and Muscle Performance

ABSTRACT & COMMENTARY

Synopsis: *Androstenedione supplementation does not increase serum testosterone concentrations or enhance skeletal muscle adaptation to training.*

Source: King DS, et al. *JAMA* 1999;281:2020-2028.

Androstenedione, a precursor to testosterone, is normally produced by the adrenal glands and testes and is converted to testosterone. Androstenedione is also produced by some plants and has been marketed as a product to increase blood testosterone levels and to be used as a "natural" alternative to anabolic steroid use. However, whether androstenedione actually increases blood testosterone or produces anabolic androgenic effects or has toxicity is not known. It is also known that androstenedione may be converted to estrogen directly. King and associates from the Exercise Biochemistry Laboratory at the University of Iowa conducted an eight-week randomized, controlled study of 20 healthy, normotestosterogenic men 19-29 years of age who performed eight weeks of whole-body resistance training. The subjects were randomized to receive either 300 mg/day of androstenedione or placebo. Levels of serum-free testosterone and total testosterone were not increased by androstenedione administration. Serum estrone increased significantly in the treatment group. No significant differences in skeletal muscle adaptation were seen between the two groups. However, there were no changes in the liver function tests of control or treatment groups. King et al conclude that eight weeks of androstenedione supplementation does not increase serum testosterone concentrations or enhance skeletal muscle adaptation to training.

COMMENT BY MYRON GENEL, MD, FAAP

Clinicians should welcome this study, since it provides some counterbalance to the "hoopla" that accompanied the use of androstenedione as a "nutritional supplement" to increase athletic performance.

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While promotional materials for androstenedione have been popular for some time within the fitness and muscle-building communities, much of the current hype stems from the disclosure by Mark McGwire during his record-setting home run output during the 1998 baseball season that he had been using androstenedione as a supplement to a rigorous strengthening program. Billed as a "natural" precursor of testosterone, androstenedione sales have boomed, especially among athletes who believe this is a safe alternative to anabolic steroids. The *JAMA* study, designed and performed by a group highly skilled in both medicine and athletics, demonstrates quite nicely not only that androstenedione administration does not increase serum testosterone levels but also that it is a precursor to naturally circulating estrogens. This may be particularly significant for male athletes during adolescence, when they are especially prone to develop gynecomastia. It has been common for me to see fairly accomplished adolescent male athletes who did not shower with their teammates because of embarrassment over presumably natural gynecomastia. Since the *JAMA* study failed to detect any difference in muscular response to resistance training, albeit over a relatively short eight-week period, perhaps clinicians can use this finding to dissuade adolescents from taking androstenedione as well as other putative enhancers of athletic performance. However, whether this advice will be accepted is dubious, for I am convinced that many dedicated athletes from junior high school on will consider doing or taking almost anything they believe may enhance their performance—even marginally. (*Dr. Genel is Professor of Pediatrics [Endocrinology], Yale University School of Medicine.*) ❖

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Dietary Supplement Use Underreported in the Office

ABSTRACT & COMMENTARY

Synopsis: *In this study, half the patients who took dietary supplements and almost half who took nonprescription medications did not report them to their health-care provider on the written questionnaire, even though this information was requested.*

Source: Hensrud DD, et al. *Mayo Clin Proc* 1999;74:443-447.

To compare the use of dietary supplements and nonprescription medications, the researchers conducted a prospective study of 200 subjects randomly selected from patients undergoing a periodic health examination. Written information on self-reported use of supplements and nonprescription medication was obtained as part of a comprehensive medical questionnaire. Subjects were then interviewed and asked about usage and reasons for usage.

The prevalence of the use of dietary supplements was 30.5% by written self-report in comparison with 61% reported during the structured interview. Use of nonprescription medication on the questionnaire was 24.5%; reported use when interviewed was 42.5%. Multivitamins (41.5%), vitamin E (24%), and vitamin C (23%) were the most common dietary supplements taken; aspirin (16.5%) and ibuprofen (13%) were the most common nonprescription medications taken. Most frequently, patients indicated that they were using supplements to promote health.

Half the patients who took dietary supplements and almost half who took nonprescription medications did not report them to their health care provider on the written questionnaire, even though this information was requested. Patients should be specifically and orally asked about usage.

COMMENT BY JOHN La PUMA, MD, FACP

These Rochester, Minnesota, investigators achieved an

83% response rate from both community residents and from executive patients. Ninety-nine percent of their community patients were white; 84% of the executives were male; overall, 62% were male. Community patients appeared to use nonprescription medications but not dietary supplements less often than did executives. These data were not analyzed for statistical significance, and educational and socioeconomic data about each group were not reported. Most patients took supplements to "promote health," and many took them to "prevent disease"—only two of 122 respondents took them to treat disease.

Why isn't a questionnaire enough to get accurate information? Patients may forget they are taking supplements, forget to record supplement names on a lengthy questionnaire, be unsure about how or whether to tell, consider them unimportant to their visit, or fear ridicule or embarrassment. In this study, a nonphysician asked about supplements, person to person—all it took to double the number of accurate responses.

Data from the 1992 National Health Interview Survey showed that 24% of the U.S. population used vitamin and mineral supplements daily. Similar data gathered since then suggest accelerated use. The boom in supplements started with the 1994 Dietary Supplement Health and Education Act, which essentially deregulated the area.

Ask the patient what he or she is taking, even if your previsit written assessment asks patients directly. Supplements should be considered medication—by patients and providers. (*Dr. La Puma is Professor of Nutrition, Kendall College, Director C.H.E.F. Clinic, C.H.E.F. Skills Research, Alexian Brothers Medical Center, Elk Grove Village, Ill.*) ❖

Raloxifene and the Prevention of Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The Multiple Outcomes of Raloxifene Evaluation is a large, multicenter trial of the antiestrogen, raloxifene, in postmenopausal women with osteoporosis. Breast cancer incidence was reduced by 76% in the groups receiving raloxifene.*

Source: Cummings SR, et al. *JAMA* 1999;281:2189-2197.

Raloxifene hydrochloride is a selective estrogen receptor modulator (SERM) that has anti-estrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipids, and coagulation proteins. Cummings and colleagues report the results of a large clinical trial of this agent in postmenopausal, osteoporotic women with the outcome of interest being the development of breast cancer.

The Multiple Outcomes of Raloxifene Evaluation (MORE) study included a total of 7705 postmenopausal women, younger than 81 years (mean age, 66.5 years) with osteoporosis, defined by the presence of vertebral fractures or femoral neck or spine T-score of at least 2.5 S.D.s below the mean for young healthy women. Women with a history of breast cancer or who were taking estrogen were excluded. Enrolled volunteers received two pills per day. They would receive either raloxifene 60 mg twice a day, raloxifene 60 mg once a day and placebo once per day, or placebo twice a day. Of the 5129 women who received raloxifene, 13 cases of breast cancer occurred over the three years of the study. In contrast, there were 27 cases among the 2576 women assigned to placebo (relative risk, 0.24; 95% confidence interval, 0.13-0.44). Raloxifene decreased the risk of estrogen receptor-positive breast cancer by 90%, but had no apparent effect upon the development of estrogen receptor-negative, invasive breast cancers.

In this study, raloxifene was generally well tolerated. The primary untoward effect was hot flashes, but compliance remained high, and the rate of patients withdrawing from study was comparable among the three groups.

There was no increased endometrial cancer in the raloxifene-treated women, although there was a slightly increased endometrial tissue thickness by transvaginal ultrasonography (performed on a subset of volunteers, n = 1781). However, there was an increase in the risk for thromboembolic disease. By 40 months of follow-up, there was a higher rate of deep venous thrombosis (38 cases, 0.7%) and pulmonary embolus (17 cases, 0.3%) in the raloxifene-treated individuals when compared to the placebo control group (5 cases of venous thrombosis, 0.2% and 3 cases, 0.1% of pulmonary embolus).

Thus, among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during the three years of treatment and the toxicity was considered manageable.

COMMENT BY DAN L. LONGO, MD, FACP

The prototype anti-estrogen, tamoxifen, was shown in the Breast Cancer Prevention Trial (BCPT) to be effective in the primary prevention of breast cancer in high-risk individuals (older, with family history, etc.).[1] In a group of patients with a risk of about 1.66% or greater in five years, based on their individual profile of prognostic factors, the risk of developing breast cancer was reduced by about 50% by tamoxifen. Although earlier, smaller studies had failed to show any benefit for tamoxifen in

primary prevention, there is confidence in the BCPT findings because of the scope and size of the study and the robust findings.[2,3] Enthusiasm for the development of alternative anti-estrogens was based upon some of the toxicity of long-term tamoxifen treatment, including deep vein thrombosis and endometrial cancer. Raloxifene offers the theoretical advantage of having anti-estrogenic functions at the endometrium (and breast) while functioning as an estrogen agonist at bone.[4]

This clinical trial, conducted at 180 centers in 25 countries (but mainly in the United States and Europe) effectively evaluated a large number of patients by using a fairly simple clinical trial design. Individuals were not at unusually high risk for breast cancer, except for their age. They were not selected for family history or by other risk factors. In fact, breast cancer has been reported to be less common in women with osteoporosis, perhaps related to their more complete or long-standing estrogen-deficient status. Yet, once again, a robust reduction in the development of new cancers was observed. As expected, no enhanced endometrial cancer was observed. There was an increase in deep venous thrombosis and pulmonary embolus. Although data were not shown in this regard, the individuals enrolled on this trial (all with significant osteoporosis) did have decreased vertebral fracture (but not fracture at other sites). Thus, raloxifene may prove to be more useful than tamoxifen in the primary prevention of breast cancer. It appears that its efficacy is at least comparable, and it may be better tolerated (with less endothelial proliferation) than tamoxifen. Comparisons in other aspects of health are also needed. Will raloxifene have the same (or better) salutory effects on serum lipids and cardiovascular end points? None of the anti-estrogens have been evaluated for their effect on cognitive function, yet hormone replacement therapy has been shown to promote cognitive function and reduce the incidence of Alzheimer's disease. Will the anti-estrogens and SERMs promote cognitive decline? Longer term and more comprehensive studies are needed to determine if this reduction in breast cancer incidence will be diminished with time as the estrogen-receptor-bearing tumors become resistant to the hormonal intervention and to evaluate the influence of the intervention on all-cause morbidity and mortality. (*Dr. Longo is Scientific Director, National Institute on Aging, Baltimore, MD.*) ❖

References

1. Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388.
2. Veronesi U, et al. *Lancet* 1998;352:93-97.
3. Powles T, et al. *Lancet* 1998;352:98-101.
4. Delmas PD, et al. *N Engl J Med* 1997;337:1641-1647.

Mirtazapine for Concurrent Depression and Anxiety

ABSTRACT & COMMENTARY

Synopsis: *This small open study suggests that the antidepressant mirtazapine (Remeron) may be effective in patients with both depression and generalized anxiety disorder.*

Source: Goodnick PJ, et al. *J Clin Psychiatry* 1999;60: 446-448.

A high proportion of patients with depression have comorbid anxiety disorder, which is associated with increased severity, poorer outcome, and increased risk of suicide. Selective serotonin reuptake inhibitors (SSRIs), nefazodone (Serzone), venlafaxine (Effexor XR), and tricyclic antidepressants (e.g., imipramine) have been shown to be efficacious for these comorbid disorders. Mirtazapine (Remeron) is a relatively new antidepressant that enhances both noradrenergic and serotonergic transmission while simultaneously antagonizing postsynaptic 5-HT2 and 5-HT3 receptors. Post synaptic 5HT2 antagonism may limit activation and contribute to its anxiolytic and sleep-enhancing properties. Post synaptic 5HT3 antagonism is a pharmacologic target for treating nausea. For example, odansetron (Zofran) is a post synaptic 5HT3 antagonist.

In the current study, 10 patients with major depression comorbid with general anxiety disorder, and without any other Axis I diagnosis, received mirtazapine 15 mg QHS for one week, 30 mg QHS for three weeks, and then 45 mg QHS for four weeks. Assessments were carried out at baseline, 1, 2, 4, and 8 weeks of therapy, including the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

There was significant improvement in scores on all rating scales used with improvement noted after the first week of therapy and continuing to improve over the eight-week period. A 50% reduction in the HAM-A score from baseline occurred for three patients after one week, five patients after four weeks, and all 10 patients at eight weeks. The most common adverse events were sedation in four patients (mostly occurring early) and blurred vision in two patients. Side effects common to SSRIs (e.g., sexual dysfunction, insomnia, gastrointestinal distress, diarrhea, and agitation) were not noted with mirtazapine.

COMMENT BY DONALD M. HILTY, MD

It appears that mirtazapine (Remeron) is a viable option for depression with anxiety, although the current findings must be replicated with a suitable double-blind, placebo-controlled design and with a larger number of subjects. SSRIs and nefazodone are the treatment of choice for these patients in the primary care setting, though with further trials this may well be reconsidered. Mirtazapine may have a valuable place in the treatment of these patients since, like nefazodone, it avoids many typical side effects of SSRIs because it antagonizes post synaptic 5HT-2. Its most significant side effects appear to be sedation and weight gain, both of which can be of marked severity in some patients early in treatment. Interestingly, in open trials the sedation appears less at 30 mg QHS than 15 mg QHS; many clinicians start at the higher dose accordingly. *(Dr. Hilty is Assistant Professor of Clinical Psychiatry, University of California—Davis, Sacramento, CA.)* ❖

Is Digoxin Safe Post-MI?

ABSTRACT & COMMENTARY

Synopsis: *Digoxin is not safe in AMI patients. Beta blockers are a better alternative for the long-term treatment of supraventricular tachycardias and heart failure after AMI.*

Source: Spargias KS, et al. *Lancet* 1999;354:391-392.

Although digoxin has been proven safe in chronic heart failure patients, its safety in the acute myocardial infarction (AMI) setting is controversial. Thus, Spargias and colleagues evaluated the outcomes associated with nonrandomized digoxin treatment in the Acute Infarction Ramipril Efficacy (AIRE) study, which entered patients 3-10 days post-AMI. At entry, 12% of the 1986 AIRE patients were on digoxin. These patients were older, more likely to be female (32% vs 26%; $P = 0.05$), and less likely to be on beta blockers (7% vs 24%; $P < 0.001$). Also, they had lower ejection fractions (32% vs 40%; $P < 0.001$), were more likely to have anterior AMIs, and be in overt heart failure. Not surprisingly, digoxin use was associated with increased total mortality. Using a Cox's proportional hazard model to keep confounding variables to a minimum, digoxin remained a significant independent predictor of increased total mortality (hazard ratio 1.4, CI 1.07-1.86, $P < 0.02$). Also, digoxin was associated with an increased risk of sudden death (1.67, 1.09-2.56, $P = 0.02$). Spargias et al conclude that digoxin is not safe in AMI patients and suggest that beta blockers are a better alternative for the long-term treatment of supraventricular tachycardias and heart failure after AMI.

COMMENT BY MICHAEL H. CRAWFORD, MD

The profound differences in the characteristics of the patients on digoxin vs. those not is a challenge to any statistical device to eliminate confounding variables. Also, we do not know how many of these patients were on digoxin before their AMI or were started on it after their AMI but before entry into AIRE. The latter group may be at particularly high risk of mortality. Despite these difficulties with a nonrandomized retrospective analysis, there seems to be little evidence that digoxin is first-line therapy for any indication in AMI. Whether it is actually harmful would require a prospective trial, which will never be done. Thus, digoxin is a second- or third-line alternative to rate lowering calcium blockers or beta blockers for rate control in atrial fibrillation and to angiotensin converting enzyme inhibitors or beta blockers for heart failure complicating AMI. (*Dr. Crawford is Robert S. Flinn Professor, Chief of Cardiology, University of New Mexico, Albuquerque.*) ❖

Pharmacology Update

Synthetic Conjugated Estrogens, A Tablets (Cenestin—Duramed)

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

In the business world, as in life, be careful what you wish for. Wyeth-Ayerst, the manufacturer of Premarin, learned this last month when the FDA approved a New Drug Application (NDA) for Duramed's conjugated estrogen, A (Cenestin). Wyeth had successfully blocked Duramed's application of an Abbreviated New Drug Application (ANDA)—a request for generic equivalency to Premarin in 1997, when it proved that Duramed's product did not contain all the estrogenic components present in Premarin. Duramed retooled and applied to the FDA as a unique drug, calling its product "conjugated estrogens, A" to distinguish it from conjugated estrogens. Approval was granted in March for short-term use in the treatment of vasomotor symptoms. Duramed's conjugated estrogens A is a mixture of nine synthetic estrogenic substances derived from plant

sources, as opposed to Premarin, which is derived from the urine of pregnant mares and contains 10 identified and quantified estrogenic compounds.

Indications

Cenestin is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause.

Dosage

Cenestin is supplied as 0.625 mg and 0.9 mg tablets. The recommended initial dose is 0.625 mg per day and may be titrated up to 1.25 mg. The lowest dose should be used that would adequately control vasomotor symptoms associated with menopause.

Potential Advantages

Synthetic conjugated estrogens are derived from plant sources—not from pregnant mare's urine. Animal rights groups such as PETA have objected to the treatment of these pregnant mares. There may also be a patient preference for product derived from plants than from animals.

Potential Disadvantages

Cenestin is not identical to Premarin. While Cenestin contains 9 of the 10 known estrogenic substances contained in Premarin, it does not contain delta 8,9-dehydroestrone sulfate and possibly other unidentified estrogenic and progestational agents.[2] It is not certain if Cenestin is pharmacologically "identical" to Premarin. Cenestin is currently approved for short-term treatment of vasomotor symptoms associated with menopause but not for the treatment of osteoporosis. Cenestin is currently only available in two doses, 0.625 mg and 0.9 mg, while Premarin is also available in 0.3 mg- and 1.25 mg-strengths.

Comments

Cenestin is the first synthetic conjugated estrogen approved by the FDA. It has been designated as conjugated estrogens A, and subsequent products will be designated as B, C, D, etc.[3] Its approval was based on a randomized, placebo-controlled multicenter trial in patients with vasomotor symptoms.[1] One hundred twenty women were randomized to receive placebo or Cenestin 0.625 mg daily. The dose was titrated upward (2 × 0.625 mg) or reduced (0.3 mg) as necessary. Efficacy was assessed at four, eight, and 12 weeks. Results have not been published; however, the product labeling stated that a reduction in moderate-severe vasomotor symptoms occurred at all time points.[1] There are no comparative trials with Premarin; therefore, dose equivalence is not known. In the placebo-controlled trial, 77% of patients required two 0.625 mg-tablets to control symptoms. This compares to the recommended dose of Premarin to treat these symptoms.

The wholesale cost for Cenestin 0.625 mg is $0.42 per tab, which is comparable to Premarin $0.42. However, if patients need a 1.25 mg-dose (77% needed that dose), then Premarin is less expensive ($0.59) since there is no 1.25 mg-strength for Cenestin.

Clinical Implications

Cenestin provides an alternative to Premarin as well as other estrogens such as estradiol. Premarin has the lion's share of the market, estimated to be about $2 billion yearly. Wyeth Ayerst has aggressively opposed the approval of Cenestin as a generic equivalent to Premarin, contending that delta 8,9-dehydroestrone sulfate and unidentified components of Premarin contribute to its pharmacologic activity.[1] After much debate, the FDA did conclude that delta 8,9-dehydroestrone sulfate is active and may contribute to the overall effect of Premarin. The magnitude of the effect has not been determined. The contribution of other unidentified components has also not been determined. There are currently no comparative trials between Premarin and Cenestin and none is required by the FDA. Until the components of Premarin have been adequately characterized, the FDA would only consider approving a generic version if it came from the same natural source (i.e., pregnant mare's urine). However, synthetic versions may be approved as new drugs. Cenestin is effective for the short-term treatment of vasomotor symptom, but its long-term effectiveness for indications such as osteoporosis is still uncertain. ❖

References

1. Cenestin Product Information. Duramed Pharmaceutical, Inc. March 1999.
2. Woodcock J. CDER. FDA Memorandum. May 5, 1997.
3. FDA Report, The Pink Sheet. March 29, 1999.

CME Questions

14. In developing a primary breast cancer prevention strategy, raloxifene offers a theoretical advantage over tamoxifen based upon:

a. its proven superiority in preventing estrogen-receptor breast cancer.
b. its reduced stimulatory effect on the uterine endometrium and, therefore, a reduced potential to induce endometrial cancer
c. its proven superiority in preventing bone loss in patients with breast cancer.
d. its better tolerability and greater patient compliance profile.

By Louis Kuritzky, MD

Hyponatremia: Evaluating the Correction Factor for Hyperglycemia

In 1949, seldin and tarail reported that elevated glucose resulted in a lower serum sodium concentration, which they attributed to a shift of water to the extracellular space due to the osmotic effect of glucose. At that time, the correction factor of 2.8 was suggested (i.e., it was stated that for every 100 mg/dL increase in blood glucose over the normal level of 100, a drop of 2.8 in sodium would be seen). This factor evolved based upon the assumption that 100 mg/dL of glucose (= 5.6 mmol) would have a similar osmotic behavior as 2.8 meq of sodium (= 5.6 mosm NaCl). Evolution of different theoretic concerns has prompted suggested revision of this correction factor so that reported conversion numbers range from 1.2-2.0.

To evaluate the effect of hyperglycemia on serum sodium concentration, Hillier and colleagues studied six healthy patients by suppressing insulin through somatostatin infusion, coupled with high-dose glucose infusion to achieve a plasma glucose of at least 600 mg/dL in less than one hour's time. Restoration of glucose to normal with insulin infusion followed. Serum sodium and plasma glucose were measured simultaneously every 10 minutes.

The response of serum sodium depression to acute hyperglycemia was essentially immediate; restoration of the serum sodium in response to serum glucose normalization was equally acute. Overall, a 2.4 meq/L sodium change was seen per 100 mg/dL glucose elevation. However, this change was not uniform (e.g., in blood sugars < 400 mg/dL, the conversion factor was 1.6, whereas for sugars > 440, the conversion factor was 4.0). Hillier et al note that the conversion factor of 2.4 is perhaps the more useful tool, since at severe levels of hyperglycemia, in which correction of sodium level is most important, this number is more accurate than the 1.6 conversion factor currently in use. ❖

Hillier TA, et al. Am J Med 1999;106: 399-403.

Transcutaneous Nitroglycerine in the Treatment of Erectile Dysfunction

The role of nitric oxide (no) as an important neurotransmitter responsible for dilation of penile arteries and relaxation of sinusoidal chambers of the corpora cavernosa and corpus spongiosum to allow erection is well defined. Nitroglycerin is known to enhance NO availability and leads directly to NO formation. Case reports of beneficial effects of topical nitroglycerin on erectile function have encouraged further evaluation of this modality.

This study evaluated 18 men with erectile dysfunction of a variety of etiologies. This double-blind placebo-controlled trial evaluated the erectile response to trandsdermal application of nitroglycerin by means of a Rigiscan monitor in the laboratory; a home study portion of the trial assessed patient-reported success in achieving a good, moderate, or no effect in response to topical nitroglycerin.

In this study, transdermal nitroglycerin did not demonstrate activity greater than placebo in either the laboratory or the home setting. Additionally, headache, the most frequently reported side effect of nitrates seen in cardiovascular use, was the most commonly reported adverse event in this group, including a female sex partner who also suffered post-coital headache attributed to nitroglycerin.

Gramkow and associates conclude that nitroglycerin transdermally is not superior to placebo for treatment of erectile dysfunction. ❖

Gramkow J, et al. Int J Impotence Research 1999;11:35-39.

Occult Vitamin D Deficiency

European studies have shown that up to one-third of women with hip fractures have signs of osteomalacia, which is often caused by vitamin D deficiency. U.S. studies to date have demonstrated less substantial (up to 25%), but still impressive, frequency of osteomalacia with hip fracture. The current study compared the prevalence of low vitamin D levels and high PTH among subjects with acute osteoporotic fractures, compared with patients scheduled for joint replacement surgery without hip fractures (the latter group chosen to represent normal, or even below normal bone mineral density).

Among the 805 women studied, 543 were in the elective joint replacement group and 262 in the acute hip fracture group. Fifty percent of the study group with postmenopausal acute hip fractures had subnormal vitamin D levels, and 36.7% had elevated PTH. The median PTH level of women with osteoporotic fractures was 1.5 times higher than in the control group.

Leboff and associates demonstrate that postmenopausal women with acute hip fracture have a noteworthy incidence of otherwise subclinical vitamin D deficiency, with accompanying PTH elevation. Such deficits are generally remediable with supplementation. ❖

Leboff MS, et al. JAMA 1999; 281:1505-1511.

Computer Oversight

By Ken Grauer, MD

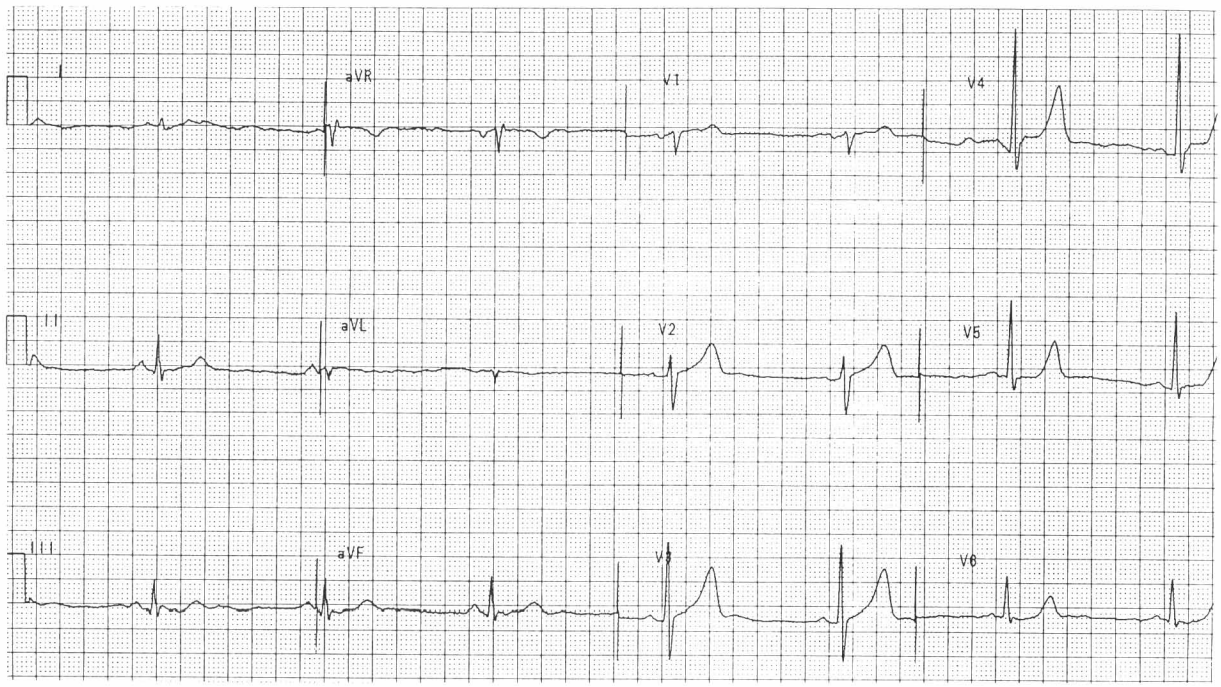

Figure. ECG obtained from a 62-year-old man who was seen in an ambulatory care setting.

Clinical Scenario. The ECG shown in the Figure generated a computerized interpretation of "sinus bradycardia—otherwise normal ECG." Do you agree with this interpretation?

Interpretation. The rhythm is sinus bradycardia at a rate of 50 beats/minute. The mean QRS axis and all intervals are normal. QRS amplitude is relatively decreased in the standard limb leads. Transition is normal and occurs between leads V_2 and V_3. There is no sign of chamber enlargement. The most remarkable finding on this tracing is the presence of tall peaked T waves in most precordial leads. In addition, the ST segment is distinctly flat in leads V_4 through V_6, instead of manifesting the normal smooth upslope with gradual transition into the T wave (as seen in leads V_2 and V_3).

Although hyperkalemia is clearly suggested by T wave appearance in this tracing, serum potassium was not increased. Other than hyperkalemia, T wave peaking in anterior precordial leads may be seen as a normal variant or as a manifestation of posterior wall ischemia.

Anterior leads typically reflect a mirror image view of ischemic events that occur in the posterior wall. The "mirror image" view of T wave peaking would be deep symmetric T wave inversion, or a pattern suggestive of ischemia. In support of the interpretation that T wave peaking in anterior precordial leads might reflect posterior ischemia is the finding of ST segment flattening in lateral precordial leads. Such ST flattening may be a subtle sign of coronary artery disease. Clinical correlation would be needed in this case to determine the relevance of these subtle but suggestive ECG signs of potential ischemic heart disease. ❖

In Future Issues:

Aspirin for Carotoid Endarterectomy