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Scoping for Knee OA Revisited: It's Still not OK

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: In knee OA, arthroscopic surgery confers no benefit.

Source: Kirkley A, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2008;359:1097-1107.

SIX YEARS AGO, *NEJM* REPORTED¹ (AND I REVIEWED²) MOSELEY'S study of the use of arthroscopy to treat knee osteoarthritis (OA). The conclusion was that patients randomized to surgery did not experience reduced pain or improved function. After the study was published, several concerns were raised, namely, the study group was composed of elderly male veterans,³ X-rays during posterior-anterior flexion in a weight-bearing position were not performed,⁴ the pain scale was not validated, and the study was underpowered.⁵

Kirkley and colleagues from the University of Western Ontario report their trial that answers those concerns. Patients had to be at least 18 years old and without large meniscal tears. They screened 277 patients for eligibility, and after appropriate exclusion, they randomized 188. Reasons for exclusion included more than 5° of misalignment, inflammatory or postinfectious arthritis, previous arthroscopy, history of major knee trauma, severe OA, and corticosteroid knee injection in the last three months, among others. Subjects were X-rayed to grade the severity of OA, received a detailed physical examination of the knee, and completed several questionnaires and clinical scoring tools, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Short Form-36 Physical Component Summary, both validated instruments.

Patients were randomized to the study group, which received optimized physical and medical therapy and arthroscopic treatment,

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or the control group which only received the physical and medical therapy. Arthroscopic therapy could involve synovectomy, debridement, or excision of meniscal degenerative tears, cartilage fragments, or chondral flaps and osteophytes. Physical therapy involved 1-hour weekly sessions for 12 weeks. Participants were also instructed in a home exercise program. Medical therapy began with acetaminophen and nonsteroidal anti-inflammatory drugs, and progressed to hyaluronic acid injection if necessary. Patients were also offered oral glucosamine. Patients were seen periodically by a nurse who was blind to treatment, and all patients wore a neoprene sleeve over their knees to hide the study groups' surgical scars. There were 94 patients assigned to surgery; two withdrew consent and six declined to undergo arthroscopy. The same number was assigned to the control group. Eight withdrew consent. The two groups were similar in all respects. They were in their late 50s and predominantly female, with a body mass index of 31 kg/m².

At the 3-month check, the WOMAC scores in the surgery group showed greater improvement than the control group. After that and through two years of follow-up, there were no significant differences between the groups. Both groups showed improvement. The investigators performed subgroup analysis for patients who were having mechanical symptoms of catching or locking; again, there was no difference between the groups.

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When physical function, pain, or quality of life was compared, the groups were similar.

COMMENTARY

Medicine has a shameful history of adopting new technology and medications without thorough testing. "First, do no harm" has been replaced by "We do it because we can." Marx, in his editorial,⁶ concludes "osteoarthritis of the knee (in the absence of a history and physical examination suggesting meniscal or other findings) is not an indication for arthroscopic surgery and indeed has been associated with inferior outcomes after arthroscopic knee surgery." Since patients in both groups improved with physical and medical therapy, that should be our mainstay of treatment, along with encouraging our patients to lose weight and to walk regularly.

By the way, think twice about ordering an MRI of the knee for patients with unclear knee symptoms. In a companion article⁷ in this issue, Englund and colleagues present their study of 991 middle-aged and elderly people who had MRIs of their right knee. Among women 50-59 years old, 19% had a meniscal tear or destruction, and for men 70-90 years old, the prevalence was 56%. Most (61%) did not have any knee symptoms during the previous month. Among people with radiologic evidence of OA, there was no significant difference in meniscal injury between those with symptoms (63%) and those without (60%). Among people without radiologic evidence of OA, 32% of those with symptoms had some meniscal injury, vs 23% of those without, which was statistically significant. So if your patient presents with knee symptoms and you get an X-ray that does not demonstrate OA, you have a 1 in 3 chance of finding a meniscal injury on MRI, but because the baseline prevalence is 23%, there is only a 9% chance that the injury is related to the symptoms. ■

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8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Do Your Looks Matter? The Effect of Race, Culture, and Values on the Patient- Physician Relationship

ABSTRACT & COMMENTARY

By **Rahul Gupta, MD, MPH, FACP**

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Dr. Gupta reports no financial relationship to this field of study.

Synopsis: Whereas racial concordance is the primary predictor of perceived ethnic similarity, patients do value higher communication skills, which may actually result in better outcomes.

Source: Street RL Jr, et al. Understanding concordance in patient-physician relationships: Personal and ethnic dimensions of shared identity. *Ann Fam Med* 2008;6:198-205.

ONE OF THE FOREMOST GOALS FOR THE HEALTHY PEOPLE 2010 program¹ is the elimination of health disparities among different segments of the population. Reported data are clear that barriers in the patient-physician relationship contribute to racial disparities in the experience of health care.^{2,3} Since differences exist in patients' perceptions of their physicians, which can impact health care utilization, status, and outcomes, it would be prudent to identify and measure such differences in a manner such that those inequalities may be better understood.

Concordance is defined as a similarity, or shared identity, between the physician and patient based on a demographic attribute, such as race, sex, or age. Race concordance between the patient and physician is well established. Such race concordance leads to higher patient ratings of care and satisfaction.^{4,5} Much less evidence points toward gender or age concordance or the interactions thereof. Furthermore, it is yet unclear whether such concordance may lead to better outcomes rather than just improvements in patient satisfaction.

In their study, Street et al hypothesized that the link between concordance and outcomes is mediated through perceptions of relational similarity. Thus, when patients perceive a physician similar to themselves, they may feel more comfortable in trusting such a physician with recommendations, which may lead to more action on their part and better outcomes. The authors set out 3

main objectives for the study: 1) to create a self-report measure of perceived similarity, 2) to evaluate the influence of concordance by race and sex on perceived similarity alone and in the context of other factors, and 3) to examine the relationship of patients' perceptions of similarity to physicians to the quality of care outcomes.

The study included a total of 269 patients and 29 physicians recruited from 10 primary care clinics in the Houston area from private and Veterans Affairs/county hospital settings. Neither Asian patients nor Hispanic physicians participated. All spoke English and were older than 18 years of age. Patients answered a subjective set of questions, which were matched to physicians to determine traits of personal and ethnic similarity. Interaction with physicians was audio tape recorded and later coded. The data were analyzed into three groups: race concordant, race discordant (White), and race discordant (minority: Blacks and Hispanics).

Patients in racially concordant (patient and physician of same race) encounters reported more personal similarity to their doctors than did minority patients in racially discordant (patients are Hispanic or Black but physicians are of different race) interactions. Similarly, patients in racially concordant encounters saw themselves as more ethnically similar to their physicians than did minority or White patients in racially discordant visits. Also, older and more educated patients, as well as those whose physicians used more patient-centered communication, perceived themselves to be more personally similar to their physicians.

Patients who believed they were more similar to their physician with respect to personal beliefs, values, and ways of communicating reported more trust in the physician, more satisfaction with care, and a stronger intention to adhere to recommendations. On the other hand, patients' perceptions of being similar to the physician in terms of race, ethnicity, and community were not related to patient outcomes. The degree to which physicians were patient-centered in their communication not only was related to patients' perceptions of personal similarity to their doctors, but it also predicted outcomes. Regardless of race, when physicians were more informative, supportive, and facilitative, the patients were more active participants, were more satisfied with care, expressed greater trust, and had a stronger intention to adhere to recommendations.

■ COMMENTARY

This study is another example of the fact that while we may not have become an entirely racially liberated society, cultural competence plays a great role in the educational training of a physician. A physicians' communication style and perceptions do affect patient

outcomes. A patient-physician relationship must build itself on the basic concept of partnership: mutual respect, support, trust, and proper dissemination of information. Data suggest that patients are able to perceive when they are respected by their physicians and are willing to give the benefit of doubt to their physicians.⁶

As a primary care physician, I take pride in the fact that I begin any such relationship by finding common ground rather than attempting to ram my personal philosophy through each patient. I treat each patient individually, looking for a different similarity for each person I come in contact with and duly note such in my progress notes for review on subsequent visits. This builds a life-long relationship with an individual who understands that I value his/her input into our conversation and provides abundant opportunity for us to come to a mutual informed decision on any issue. Often, this is all it takes to make our patients happy and content, resulting in improved outcomes and adherence to recommendations.

It is interesting that data have also shown that physicians who reported a patient-centered orientation to the doctor-patient relationship were also more patient-centered in their communication.⁷ In other words, it is basically a matter of setting your mind to it. While some may feel that current and past data could be justified to demand training more physicians from a certain ethnic group to “pair up” with patients of a similar ethnic group, what is imperative is that we emphasize the cultural competency and communication skills components of developing physicians. ■

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Estrogen Therapy and Gastroesophageal Reflux

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG, AGAF

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Dr. Robinson reports no financial relationship to this field of study.

Synopsis: Estrogen treatment (but not estrogen given along with progestin) seems associated with gastroesophageal reflux (GER) in postmenopausal women. Weight gain increases risk.

Source: Zheng Z, et al; Women's Health Initiative Investigators. Effects of estrogen with and without progestin and obesity on symptomatic gastroesophageal reflux. *Gastroenterology* 2008;135:72-81.

HORMONAL ELEVATIONS IN PREGNANCY (ESTROGEN and progesterone) have long been believed to be associated with GER. Studies of hormonal effects on GER have been inconclusive in the past. In this study, postmenopausal women were studied at 40 U.S. clinical centers. Women with hysterectomies (n = 10,739) were randomly assigned to 0.625 mg of conjugated equine estrogen (Premarin®) or placebo. Women without hysterectomies (n = 16,608) received either the same estrogen dose along with 2.5 mg medroxyprogesterone acetate daily (Prempro™) or matching placebo. More than 90% of women had available baseline data and data at one year on GER symptoms. After a year, 4.2% of women on estrogen had new moderate-to-severe symptomatic GER vs 3.1% receiving placebo (OR 1.35; 95% CI, 0.99-1.85). This strong trend implies a number needed to harm of 96 women. Estrogen plus progesterone had no effect on GER risk. Obese women (BMI > 40 kg/m²) had double the risk of incident moderate-to-severe symptomatic GER at one year with similar GER-promoting effects seen with both waist circumference and waist to hip ratio. Weight loss had a beneficial effect in terms of the reduction of incident symptomatic GER.

■ COMMENTARY

As the authors themselves note, this study dealt only with oral hormone therapy in a single dosage. Only a single year was assessed in this data presentation. High levels of GER symptoms were present in all groups at baseline (42% in the estrogen trial and 35% in the women receiving estrogen and progesterone). This

prevalence of GER is consistent with a number of previous epidemiologic studies. Increases in incident moderate-to-severe GER symptoms, even in the estrogen group, were modest at best. At baseline, moderate-to-severe heartburn was already present in 13% of those in the prospective estrogen arm and in 9% of the group which was to receive estrogen and progesterone or the matching placebo. In the past, most experts assumed that the culprit hormone causing GER in pregnancy was most likely to be progesterone. This study (the richly productive Women's Health Initiative or WHI) did not support this historical premise, and the conclusion that estrogen alone might be the basis for GER is at least gently supported. The most important finding from this portion of the WHI is the corroboration of other data that have strongly associated BMI and waist circumference with GER along with the premise that weight loss can significantly lower the risk of GER symptoms and the complications of gastroesophageal reflux disease. Perhaps future investigations will help elucidate the mechanisms for the effects of hormones on gastroesophageal function. Meanwhile, it seems reasonable to add the possible provocation of GER to the risk profile of estrogen therapy. ■

Pharmacology Update

Tetrabenazine Tablets (Xenazine®)

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

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Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED THE FIRST DRUG FOR THE treatment of Huntington's disease. Tetrabenazine selectively binds to central nervous system vesicular monoamine transporter sites (VMAT2), resulting in depletion of serotonin and monoamine from nerve terminals. The drug is marketed by Prestwick Pharmaceuticals, Inc., as Xenazine®.

Indication

Tetrabenazine is indicated for the treatment of chorea associated with Huntington's disease.¹

Dosage

Tetrabenazine is available as 12.5 mg and 25 mg tablets. The recommended starting dose is 12.5 mg taken in the morning. The dose may be increased to 25 mg daily (12.5 mg twice daily) after one week. Titration may continue at weekly intervals at 12.5 mg increments. Doses of 37.5-50 mg should be broken into three times daily dosing with no single dose greater than 25 mg. If further titration > 50 mg daily is indicated, the increment is 25 mg daily. Doses greater than 50 mg should not be given without CYP2D6 genotyping. The maximum dose is 100 mg daily (37.5 mg three times daily). For patients who are poor metabolizers (i.e., do not express CYP2D6), the maximum dose is 50 mg daily.¹

Potential Advantages

Tetrabenazine showed statistically significant improvement in chorea burden as well as improved clinical global improvement.^{1,2}

Potential Disadvantages

Tetrabenazine produces dose-dependent adverse events that include depression, fatigue, insomnia, sedation/somnolence, akathisia, restlessness, and disability.¹ It can increase the risk of suicidal thought and behavior. Most frequent adverse events compared to placebo are akathisia (19% vs 0%), sedation/somnolence (31% vs 3%), and Parkinson symptoms (15% vs 0%). Other adverse events include dysphagia, hypotension, hyperprolactinemia, small QTc prolongation, and neuroleptic malignant syndrome. Tetrabenazine should be avoided in patients at risk for cardiac arrhythmias, or patients who are taking a drug that may prolong QTc.

Comments

Tetrabenazine selectively and reversibly binds to VMAT2, resulting in depletion of monoamines in the CNS. The drug has been available since the 1950s and was initially studied as an antipsychotic but more recently for hyperkinetic movement disorders such as chorea, tics, and tardive dyskinesia.³ The antichorea effectiveness of tetrabenazine was shown in a randomized controlled trial in 84 ambulatory patients with Huntington's disease.^{1,2} Patients were independently ambulatory, with a screening total functional capacity greater than 5, and total maximum chorea score of 10 or greater (i.e., sum of the maximal chorea scores for face, buccal-oral-lingual, truncal, and each extremity from the motor subscale of the Unified Huntington's Disease Rating Scale [UHDRS]). Patients were randomized to tetrabenazine or placebo. The study duration was 12 weeks with a 7-week titration period, 5-week maintenance period, and a

1-week washout period. Tetrabenazine was started at 12.5 mg, and increased 12.5 mg weekly until the desired antichorea effect was achieved, 100 mg daily, or tolerability. The primary outcome was a reduction in the total maximal chorea score of the UHDRS. The secondary outcome was clinical global improvement. Tetrabenazine produced a reduction of 5 units compared to 1.5 units for placebo. The adjusted mean affect size (-3.5 units) represented a 23.5% reduction in chorea severity. There was also a statistical improvement in clinical global improvement. Five patients withdrew from the study group (9.3%) compared to none in the placebo group. Two occurrences of suicide or suicide ideation occurred in the study group and none in the control group. During the washout period, the mean total chorea score returned to baseline.

Clinical Implications

Huntington's disease is an inherited autosomal dominant disease with about 250,000 individuals in the United States affected or at risk of inheriting this fatal disease.⁴ This disease is characterized by progressive motor, cognitive, and behavioral symptoms.^{1,4,5} Antipsychotics, NMDA-antagonists, and other drugs have been used to treat chorea with limited success. Tetrabenazine showed improvement in chorea in a small randomized placebo-controlled study. However, benefit may be limited as functional capacity worsens, chorea lessens, and dystonia intensifies.⁶ Tetrabenazine does not appear to improve other symptoms and may increase the risk of depression and suicidal thoughts. Depression is the most frequent psychiatric symptom in Huntington's disease. ■

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CME Questions

36. In the study of arthroscopic surgery for osteoarthritis, compared to the control group, patients in the study group had:

- a. a higher average weight.
- b. no improvement in pain.
- c. greater improvement in function.
- d. greater improvement in quality of life.

37. Patients are more active participants, more satisfied with care, express greater trust, and have a stronger intention to adhere to recommendations when their physicians have all of the following characteristics except:

- a. belong to the same race.
- b. communicate well.
- c. more informative.
- d. more supportive and facilitative.

38. In the WHI study, hormonal exacerbation of GER was associated with:

- a. estrogen plus progesterone therapy.
- b. estrogen therapy alone.
- c. progesterone therapy alone.
- d. estrogen plus progesterone therapy in women with weight loss > 10% during the study.
- e. estrogen therapy in women with weight loss > 10% during the study.

Answers: 36. (b), 37. (a), 38. (b).

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

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Cognitive Impairment Progression Blunted by Exercise

Source: Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* 2008;300:1027-1037.

CLINICAL TRIALS OF PHARMACOTHERAPY to prevent progression of cognitive decline in those with mild cognitive impairment (MCI) have been disappointing; neither cholinesterase inhibitors (donepezil, rivastigmine, galantamine), vitamin E, nor COX-2 inhibitors has demonstrated any clinically meaningful benefit in placebo-controlled MCI trials.

Observational data are consistent that regular physical activity, even if started late in life, is associated with reduced risk of dementia. Whether exercise might prevent progression in persons with MCI was the subject of this first randomized trial to address the issue.

Subjects (n = 170) with MCI between the ages of 50-77 (mean age, 68.6 years) were randomized to receive either 50-min sessions of moderate-intensity exercise (e.g., brisk walking, ballroom dancing, and swimming) three times weekly vs control (general education about health, including physical activity, diet, alcohol, and stress management). All educational materials were also provided to the intervention group. All participants (control and intervention) wore a pedometer and provided diaries of daily total number of steps. Physical activity and cognitive function were assessed at 6, 12, and 18 months after randomization.

At each assessment point, cognitive scores for the intervention group were better than the control group. The intervention group averaged approximately 6000 more steps/week than the control

group. Exercise, averaging as little as 21 min/day, reduces cognitive decline in persons with MCI. ■

Pramlintide as a Weight-Loss Adjunct

Source: Smith SR, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008;31:1816-1823.

SOMETHING THAT NEITHER MOTHER nor medical school taught us was that more than one hormone is secreted from the beta cells of the pancreas in response to rising glucose. In conjunction with insulin, the hormone amylin is released. Pramlintide is a synthetic form of amylin. The physiologic effects of amylin include slowed gastric emptying (thereby slowing the rate of glucose delivery to the intestine), suppression of glucagon, and centrally mediated satiety. For addressing obesity, there is great conceptual appeal to an agent that improves satiety.

Smith et al performed a double-blind, placebo-controlled trial of various doses of subcutaneous pramlintide (bid to tid) in obese, nondiabetic subjects, who were also receiving intensive lifestyle (diet/exercise) intervention. The initial 4-month double-blind phase was followed by a 4-month single-blind extension (for those who completed the initial phase without protocol violation).

Weight loss was dose-proportional: At 360 mg twice daily the placebo-corrected weight loss was 3.3 kg at month 4 and 7.2 kg at month 12. No safety concerns were seen. Nausea, which is also the most common adverse event seen in diabetic subjects, was mostly mild to moderate, and improved over time. Nausea is not the mechanism of action, since weight reduction was similar in those who did and did not

experience nausea. These initial data are encouraging that pramlintide may find a role in enhancing weight loss when used in conjunction with lifestyle intervention. ■

Hormone Replacement and Skin Health in Menopausal Women

Source: Phillips TJ, et al. Does hormone therapy improve age-related skin changes in postmenopausal women? *J Am Acad Dermatol* 2008;59:397-404.

AS LITTLE AS A DECADE AGO, MENOPAUSAL status alone was the ticket of admission to advocate hormone replacement therapy (HRT). The "story line" went that HRT prevented cognitive decline, improved symptoms, enhanced cardiovascular health, and preserved cutaneous health, i.e., reduced age-related wrinkles, dryness, and laxity. Unfortunately, HRT has failed to live up to many of its hopeful claims.

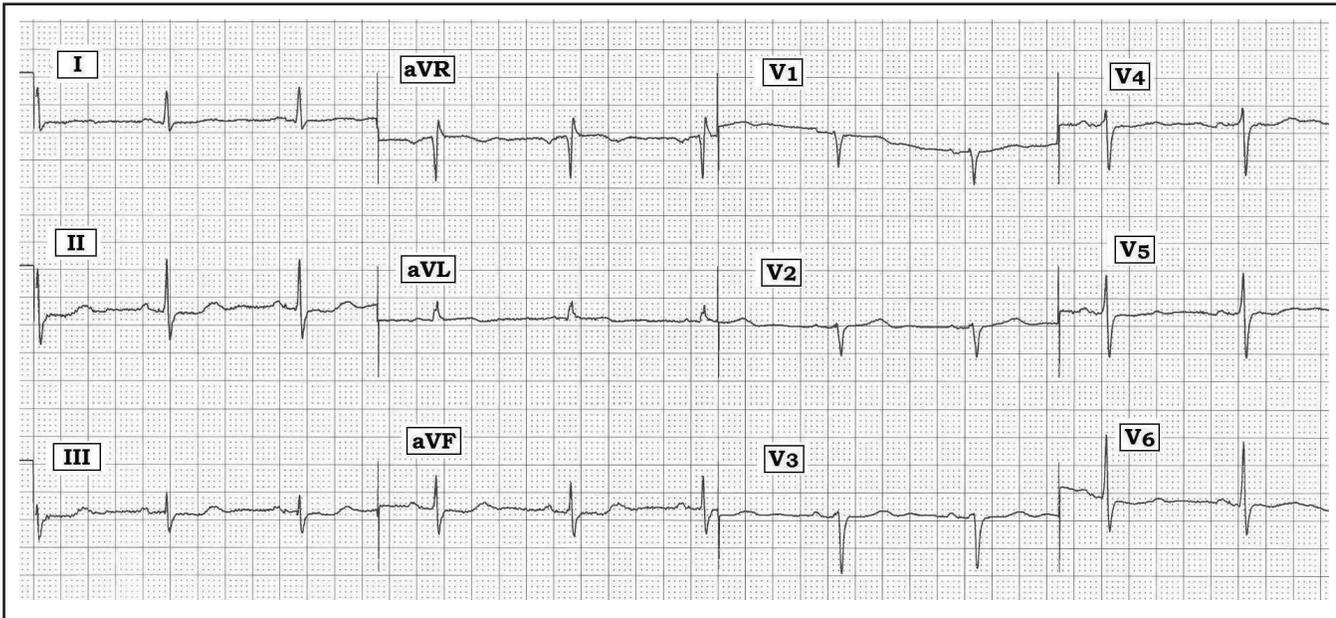
To study the effects of HRT on menopausal women's skin, 485 subjects were randomly assigned to placebo or two different HRT doses in double-blind fashion. Dermatologists evaluated skin wrinkling, laxity, and texture (as did the patients) over a 48-week interval. The mean age of the women was 54 years.

At study end, there were no statistically significant differences in any primary endpoint of the trial. When the data were analyzed for impact of baseline levels of estradiol, race, or age, no meaningful differences were found. During the trial, all study groups enjoyed some skin improvements attributable to daily application of moisturizing cream and sunscreen, but HRT added nothing to this. Claims that HRT provides reduced risk of age-related skin changes are not supported by this trial. ■

A Patient with Chest Pain

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Clinical Scenario

The ECG shown above was obtained from a patient who was seen in the office with atypical chest pain. Is there cause for concern?

Interpretation

The rhythm is sinus at a rate of about 60/min. The axis and all intervals are normal. There is no chamber enlargement. The principal findings of concern are the subtle but definitely present ST-segment depression in each of the inferior leads that occurs in association with equally subtle but nevertheless present ST-segment elevation in lead aVL. There is non-specific ST-segment

flattening in several other leads. This tracing provides an excellent example of how shape more than amount is often the key for assessing the significance of ST-T wave changes. While the amount of ST-segment deviation is minimal in this tracing—the pattern of changes seen here in a patient having chest pain could reflect acute evolving infarction (or perhaps a later phase in a patient who recently infarcted). Clinical correlation and comparison with prior tracings would be invaluable for clarifying the situation. A final point is the fact that the remote high lateral lead aVL can at times be the only lead showing ST-segment elevation with acute infarction. ■

In Future Issues:

CT Colonoscopy for Detection of Large Adenomas and Cancers

Effect of Pharmacotherapy and Decline in COPD Lung Function

Effects of Intensive Glucose Lowering in Type 2 Diabetes

Serum 25-hydroxyvitamin D and Hip Fracture Risk

The Trousseau Syndrome: Screening Cancer Patients for Venous Thromboembolism