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INSIDE

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Calcium, Bones, and the Heart

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

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

Synopsis: *A study to determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women.*

Source: Bolland MJ, et al. Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial. *BMJ.* 2008; Jan 15 ePub ahead of print.

THIS REPORT IS A SECONDARY ANALYSIS OF A STUDY THAT WAS designed to evaluate the effects of calcium supplements on bone health in post-menopausal women in New Zealand. It included 1471 women, mean age 74 years, who were randomized to either calcium or placebo. Outcomes were death, myocardial infarction (MI), angina or chest pain, stroke, and transient ischemic attack. Exclusions included being under 55 years of age, having a life expectancy of less than 5 years, already being on calcium supplements, active treatment for osteoporosis, vitamin D deficiency, ongoing liver, kidney, thyroid, or bone disease, and malignancy. The calcium supplement and placebo groups were well matched for age, weight, body mass index (BMI), blood pressure, and a variety of other measures, although there were slightly higher, statistically insignificant rates of current and former smoking, previous hypertension, previous dyslipidemia, and previous cardiovascular disease in the calcium supplementation group. Active treatment was a gram of elemental calcium citrate in a split dose. Follow-up occurred every 6 months for 5 years. At 5 years, 90% of the cohort was still being followed-up, although about 300 women in each group stopped taking the study drug. Including the drop-outs, compliance with either the active calcium or the placebo was 55% and 58%, respectively. For self-reported cardiovascular events, the group assigned to calcium had statistically more myocardial infarctions

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(45 vs 19) and "composite events" (MI, stroke or sudden death) than did those who were taking placebo (101 vs 54). However, when the reported events were adjudicated (review of hospital records and death certificates) only myocardial infarction was statistically increased in those who took calcium (24 events vs 10, $p = 0.047$). In the final analysis, after inclusion of events not reported by participants, a statistically significant increase in the number of women with any of the end points in the calcium group was no longer found. Controlling for compliance with treatment did not affect these findings. The authors conclude, "Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates. This potentially detrimental effect should be balanced against the likely benefits of calcium on bone."

COMMENTARY

I must confess that I skimmed the title and abstract of this paper with personal alarm. Many, many women take calcium supplements, and may be questioning the wisdom of doing so in the wake of this report published in a prestigious medical journal. Indeed, use of a variety of vitamins and supplements has been shown to either have no benefit or to cause actual harm in recent years. Calcium supplementation, on the other hand, has stood the test of time as being beneficial for bone health for women, particularly postmenopausal women. A recent large metanalysis[1] confirmed and synthesized what is known about calcium supplementation, and concluded, "Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D." This paper noted that the beneficial effect of calcium on reduction of fractures depends on compliance. (what doesn't?) Indeed, the parent study for the current paper2 found that calcium supplementation was associated with a reduction in bone loss over a 5-year period, but noted that compliance limits it effectiveness.

Beyond its effects on bone health, there is evidence that calcium supplementation has a salutary effect on several intermediate endpoints, including reduction in cholesterol,[3] blood pressure,[4,5] and weight.[5]

These authors have definitely taken a "cup half empty" approach to their findings. Despite lack of solid statistical evidence that calcium supplementation causes cardiovascular disease in this (or any of the other studies they reviewed), they cite the trends noted in this paper, and note, "The present data do not permit definitive conclusions to be reached in this regard but do flag cardiac health as an area of concern in relation to calcium use ... this potentially detrimental effect should be balanced against the likely benefits of calcium on bone, particularly in elderly women."

Savvy women patients may be asking you about this report and about the wisdom of continued use of calcium supplements. The data are much stronger that calcium (taken compliantly, at 1200 mg/day with vitamin D) reduces bone loss than that calcium contributes to cardiovascular disease. I'm still taking mine. ■

References

1. Tang BMP, et al. *Lancet.* 2007;370:657-666.
2. Reid IR, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med.* 2006;119:777-785.
3. Reid IR, et al. Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. *Am J Med.* 2002;112:343-347.
4. Griffith LE, et al. The influence of dietary and nondietary calcium supplementation on blood pressure—an updated metaanalysis of randomized controlled trials. *Am J Hypertens.* 1999;12:84-92.
5. Reid IR, et al. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. *J Clin Endocrinol Metab.* 2005;90:3824-3829.

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Frequency of False Positive Cardiac Catheterizations in STEMI Patients

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *The frequency of false positive cardiac catheterization laboratory activation for suspected STEMI in community practice is relatively common with 14% of patients having no clear-cut culprit coronary artery lesions and 9.5% having no significant epicardial coronary artery disease.*

Source: Larson DM, et al. "False positive" cardiac catheterization laboratory activation among patients with suspected ST segment elevation myocardial infarction. *JAMA.* 2007;298:2754-2760.

The standard 12 lead electrocardiogram (ECG) remains a critically important diagnostic tool for the emergency management of patients with acute myocardial infarctions despite its accepted limitations.[1] Time to reperfusion of occluded coronary arteries is a major determinant of outcome in patients presenting with an ST-segment elevation myocardial infarction (STEMI)[2,3] and therefore, the STEMI guidelines of the American College of Cardiology/American Heart Association recommend that emergency department (ED) physicians make the decision regarding reperfusion therapy within 10 minutes of interpreting the initial diagnostic ECG.[4] Immediate activation of the cardiac catheterization laboratory by the ED physician has been vigorously recommended as a key strategy to reduce door-to-balloon times.[5]

Because rapid reperfusion of an occluded coronary artery is indeed the most important quality metric in patients with STEMIs, the potential clinical and financial consequences associated with false alarms need to be considered.[6] Larson and his colleagues from the Minneapolis Heart Institute Foundation prospectively determined the prevalence, etiology and outcomes of "false positive" catheterization laboratory activation occurring in a consecutive series of transported patients with suspected STEMI.[7] The catheterization laboratories were located in a tertiary cardiovascular center in Minneapolis, Minnesota, which serviced 30 community and rural hospitals. A total of 1345 STEMI patients were transferred from various community hospitals located up to 210 miles from the tertiary center for facilitated percutaneous coronary intervention (PCI) according to a standardized protocol. The diagnosis and decision to activate the catheterization laboratory was made by the on-duty ED physician in each community hospital to which the patients had initially been transported. In cases of diagnostic uncertainty, the presenting ECG was faxed to an attending cardiologist for review before the catheterization laboratory was activated. Transferred patients bypassed the ED Department of the tertiary hospital and were taken directly to the catheterization laboratory. The prevalence of false-positive cardiac catheterization laboratory activation was between 9.2% and 14% depending on the definition of "false-positive" based on the anatomy of the coronary arteries determined at the time of catheterization and evaluation of the cardiac biomarker results.

COMMENTARY

Patients were enrolled in the Larson study between March, 2003 and November, 2006.[7] The recently published 2007 focused update of the ACC/AHA guidelines for the management of patients with STEMI reaffirms that if a patient is taken to a non-PCI hospital, it is appropriate to consider emergency inter-hospital transfer of the patient to a PCI-capable hospital for mechanical revascularization.[8] Among the 1335 patients referred to the tertiary catheterization laboratory, 14% had no clear-cut culprit coronary artery lesions, 9.5% had no significant epicardial coronary artery disease and 11.2% had negative cardiac biomarkers. Or course, it must be recognized that all of these patients were referred from community hospitals and there were not primary admissions to the tertiary hospital where diagnostic accuracy might have been significantly improved.

"False positive" catheterization laboratory activations theoretically should be, of course, unavoidable to some degree because of the necessary trade-offs between specificity and sensitivity since the absence of false positive activations in this study would almost certainly imply that PCI had not been provided to some patients who actually needed the procedure performed. However, in the modern era, it is quite likely that the "false positive" rates may be significantly diminished because so many EDs will likely be improving their diagnostic accuracy utilizing evolving technologies such as 64 slice ultrafast computed tomography on carefully selected STEMI

patients presenting with chest pain in whom the diagnosis is not absolutely clear-cut (ie, patients with atypical chest pain and/or who have borderline EKG and/or biochemical abnormalities); however, it should be clearly recognized that patients who demonstrate clear-cut ST segment elevations (especially if associated with enzyme elevations) are certainly not candidates for ultrafast coronary CT angiography (CTA) but rather should be immediately referred to the cardiac catheterization laboratory. CTA would almost certainly have anatomically defined the coronary anatomy in most of the 14% of patients in the Larson study, with no clear culprit of coronary artery lesions, and the 9.5% of patients who had no significant epicardial coronary artery disease but should be considered for use only in atypical chest pain patients in whom the admitting EKG does not demonstrate clear-cut ST segment elevations, and especially if the admitting troponin levels in these patients are normal. However, if any residual uncertainty exists after the ED workup of the STEMI patient is completed, referral to the cardiac catheterization laboratory immediately would be mandatory in most instances. Hopefully, Larson and his colleagues will continue their very important work and will soon be able to report on the diagnostic value of CTA in carefully selected patients in the community ED. However, it should be clearly recognized that, at this time, all chest pain patients with clear-cut ST segment elevations and/or abnormal admitting cardiac enzymes should be sent to the catheterization laboratory and should not be subjected to a diagnostic CTA.

In summary, it is quite clear that the frequency of false positive cardiac catheterization laboratory activation for suspected STEMI patients has been relatively common in community practice. However, current and ongoing improvements in imaging technology and other diagnostic improvements will undoubtedly improve patient selection, will reduce false positives with respect to cardiac catheterization laboratory activation, and ultimately will improve outcomes in the ongoing quest to rapidly open acutely occluded coronary arteries. ■

References

1. Zinetbaum PJ, et al. Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med.* 2003; 348(10):933-940.
2. Boersma E, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996;348(9030): 771-775.
3. Brodie BR, et al. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol.* 2006;47(2):289-295.
4. Antman EM, et al. ACC/AHA guidelines for the management of patients with ST elevation myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation.* 2004;110(5): 588 at 636.
5. Bradley EH, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction *N Eng J Med.* 2006;355(22):2308-2320.
6. Barbagelata A, et al. *J Electrocardiol.* 2006;39(4);S73-S74.
7. Larson DM, et al. *JAMA.* 2007;298:2754-2760.
8. Antman E, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. A report of the ACC/AHA task force on practice guidelines. *J Am Coll Cardiol.* 2008;51:210-247.

Can Your Patient's Socioeconomic Status Have an Adverse Effect On You?

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *A physicians' survey in Connecticut indicates that a patient's socioeconomic status (SES) affected their clinical management decisions.*

Source: Bernheim SM, et al. Ann Fam Med. 2008;6:53-59.

One of the top priorities for both the National Institutes of Health and the Healthy People 2010 program is to eliminate health disparities among different segments of the population. The widespread and diverse nature of healthcare disparities is well documented. Socioeconomic status (SES) influences healthcare quality and outcomes. SES is a composite

attribute, which may include features such as income, education level, insurance status, access to care, patient's beliefs and factors such as trust and communication between the patient and the healthcare provider.

In their study, the authors examine how a patient's SES influences the physicians' clinical management decisions. They achieve this task by investigating the physician perspectives on how the patients' SES ultimately influences their clinical management decisions. In this project, the authors conduct a qualitative study without any previously described theoretical framework and interviewed 18 primary care physicians from diverse backgrounds, most caring for Medicaid patients in the State of Connecticut. Most physicians (15) were randomly identified and contacted for interview and 3 additional were identified as either minority or those caring for veterans. Physician investigators interviewed all the participants and line-by-line coding was performed from which recurrent themes emerged that characterized the experiences of the participants.

When asked to characterize the low SES of their patients, most physicians included positive, negative or both descriptors. Their attributes for low SES included not only the uninsured and unemployed but also those of minority race, low educational achievement, poor social networks, and low health literacy and health behaviors as well as those who were appreciative and interested in health. Four major themes emerged from the interviews: (1) Physicians held conflicting views about the effect of patient SES on clinical management. As a common trend, the physicians stated the notion that the low SES should not influence the standard of practice. Most, however, recounted circumstances where they had to do just the opposite. (2) Physicians believed that changes in clinical management due to patient SES were made in the patient's best interest. The physicians often adjusted their expectations of the practice of medicine to the "ground zero" reality. (3) Physicians varied in the degree to which they thought changes in clinical management influenced patient outcomes. Overall, the physicians indicated that the clinical management decisions made to accommodate with the low SES could compromise outcomes but not always. (4) Physicians faced personal and financial trains when caring for patients of low SES. They often experienced a dilemma between maintaining a consistent standard of care for everyone and providing "appropriate care" which was not standard, given a patient's SES. They expressed frustration over longer time spent with these patients and questioned the sustainability of the current healthcare system.

COMMENTARY

The contribution of the magnitude of the effect of SES towards health disparity has yet to be quantified. However, it is clear that SES has a direct impact on a patient's health as well as those that provide healthcare. With the steady rise in the number of uninsured Americans, understanding this concept gains more significance now than ever before for health policy makers. Rather than blindly adopting initiatives that sound good but have yet to conclusively prove benefits such as pay for performance (P4P), we ought to be more focused on eliminating healthcare disparities. Perhaps, P4P has been relatively effortlessly accepted because it virtually serves as a self-fulfilling prophecy; in other words, it's a win-win situation for everyone. On one hand, we are able to gather "data" that progress is being made on achieving certain pre-specified "performance targets" while concurrently providing physicians incentives in place of adequate compensation. However, such policies fall short at the most fundamental level, providing care to those who need it the most.[1] These disparate populations of patients in the lower SES remain at the mercy of our ever-collapsing safety nets and the shrinking population of physicians who care for them and value service over compensation. As a result, our vacillating healthcare delivery system expects a certain standard of medical care but is unable to truly afford one for each of its citizens.

This is where I am reminded of the John Rawls' alternative distributive principle, which may have its own critics but in essence, it proposes a system that allows allocation that does not conform to strict equality so long as the inequality has the effect that the least advantaged in society are materially better off than they would be under strict equality. Thus, while we should applaud physicians such as those interviewed who are keeping the least disadvantaged over the safety net, we should simultaneously strive for a better healthcare delivery system. Healthcare should be viewed as a common social good, not just another commodity and therefore supplied as a need, not as a want.[2] It should also be clearly understood that no amount of P4P will ever improve quality or efficiency as long as healthcare disparities persist. In fact, we must be careful to ensure that such delivery system reforms do not work to widen the already existing gaps.[3,4]

References:

1. Casalino LP, et al. *Health Aff.* (Millwood). 2007;26:w405-414.
2. Franks P, Fiscella K. *J Gen Intern Med.* 2008; [Epub ahead of print].
3. McMahon LF Jr, et al. *Am J Manag Care.* 2007;13:233-36.
4. Coleman K, Hamblin R. *PLoS Med.* 2007;4:e216.

Pharmacology Update

Etravirine Tablets (Intelence™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

THE FDA HAS APPROVED, AFTER PRIORITY REVIEW, A new non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV-1 infected adults who have failed other antiretroviral agents. Etravirine (TMC125) has shown in vitro activity against NNRTI-resistant strains. It is marketed by Tibotec Therapeutics, a division of Ortho Biotech Products as Intelence.

Indications

Etravirine is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents.[1]

Dosage

The dose is 200 mg (2 x 100 mg tablets) taken twice daily following a meal.[1]

Etravirine is available as 100 mg tablets.

Potential Advantage

Etravirine is active *in vitro* against a large percent (85%) of HIV-1 strains with single amino acid substitution at reverse transcriptase positions associated with NRTI resistance including the most common (K103N). Overall, etravirine is active against 60% of NNRTI-resistant clinical isolates from clinical trials.[1]

Potential Disadvantages

Severe and potentially life threatening skin reactions, including Stevens-Johnson syndrome and erythema multiforme have been reported (<0.1%). Etravirine has the potential for numerous drug-drug interactions as it is a substrate of CYP3A4, CYP2C9, and CYP2C19, inhibitor of CYP2C9, and CYP2C19, and inducer of CYP3A4. Coadministration of etravirine with inhibitors, inducers, and substrates of one or more of these isoenzymes may affect the therapeutic effects of etravirine or the coadministered drug. Drugs that should not be coadministered with etravirine include, NNRTIs, protease inhibitors not boosted with ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, rifabutin, and St John's wort. Etravirine shows decreased susceptibility to mutant HIV-1 strains with 2 or 3 amino acid substitutions. Single substitutions at certain positions (eg, K101, K101Q) show cross-resistance between efavirenz and etravirine.[1]

Comments

The approval of etravirine was based on the 24-week results of 2 ongoing randomized, double-blind, placebo-controlled, phase 3 studies (TMC125-C206, TMC125-C216 (DUET-1 and DUET-2). Eligible patients included those with documented genotypic evidence of NNRTI resistance, three or more primary protease inhibitor mutations, viral load over 5000 copies/ml, and on a stable regimen for 8 weeks.[1,2,3] All patients received a background regimen containing darunavir/ritonavir and at least 2 investigator selected nucleoside/nucleotide

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.

reverse transcriptase inhibitor and optional enfuvirtide. They were randomized to placebo (n = 604) or etravirine at 200 mg twice daily (n = 599).

Primary outcome was proportion of patients with viral load <50 copies/ml. At week 24, 59.8% of those randomized to etravirine had virologic response compared to 40.2% for placebo. Virologic failure rates were 31.7% and 53.0% respectively. There were 9 deaths (1.5%) in the etravirine group and 16 (3.6%) in the placebo group. The discontinuation rates were 7% and 4.1% respectively. Skin and subcutaneous tissue disorders were the most common adverse events (16.9%) with Grade 2 or higher rash (9%). Serious skin reactions (Steven-Johnson syndrome, hypersensitivity reaction, erythema multiforme) have been reported albeit rarely (<0.1%). Etravirine has the potential for numerous drug-drug interactions. The long-term safety and effectiveness of Etravirine is not known. The 30-day wholesale cost for etravirine is $654.

Clinical Implications

Etravirine provides a treatment option for HIV-1 infected patients with NNRTI resistant virus. Due to the potential for multiple drug-drug interactions the combinations of antiretroviral agents that could be used with etravirine is somewhat limited. ■

References

1. Intelence Product Information. Tibotec Therapeutics. January 2008.
2. Lazzarin A, et al. *Lancet.* 2007;370:39-48.
3. Madruga JV, et al. *Lancet.* 2007;29-38.

CME Questions

8. The frequency of false-positive cardiac catheterization laboratory activation for suspected STEMI in community practice in 2003-2006:

a. is unknown.
b. is extremely low.
c is very high.
d. between 9.5 and 14%.

9. In postmenopausal women, calcium supplements:

a. reduce bone loss but cause cardiovascular disease
b. reduce bone loss but have an undetermined effect on cardiovascular disease
c. do not reduce bone loss but cause cardiovascular disease
d. do not reduce bone loss but have an undetermined effect on cardiovascular disease

Answers: 8 (d); 9 (b)

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

I've Heard of TIA, But What The Heck is a TNA?

THE FORMAL CLASSIFICATION OF cerebrovascular disorders as we know it today is only a few decades old. One of the categories named in the original 1975 classification system was "transient attacks of neurological dysfunction," comprised of transient ischemic attacks (TIA) and transient non-localizing or mixed neurologic syndromes, generally considered to be more benign. The authors have suggested that transient neurologic attacks (TNA) be subdivided into focal TNA (= TIA, usually of ischemic vascular origin) and non-focal or mixed TNA (nf/m-TNA), of diverse etiology (including, but not limited to, vascular origin). It has been observed that in clinical practice nf/m-TNA and TIA are often grouped together by primary care clinicians and neurologists alike, attesting to the sometimes "fuzzy borders" distinguishing these entities. At the same time, nf/m-TNA has generally been regarded as more "benign," and less likely to be associated with subsequent increased stroke risk.

To better study TNA, adults aged 55 years or older (n = 6,062) were followed for 60,535 person years (about 10 years each, on average). During that time a TNA occurred on 548 individuals; the incidence of nf/m-TNA (4.4/1000 person-years) and TIA (4.7/1000 person-years) was very similar. Prognostically, the hazard ratio for subsequent stroke was increased both for victims of TIA (HR = 2.4) and nf/m-TNA (HR = 1.56-2.48). TNA that are non-focal or mixed have a less benign future than has been widely appreciated. ■

Bos MJ, et al. JAMA. 2007;298:2877-2885.

Advancing Insulin Therapy in Type 2 Diabetes

WHEN ORAL AGENTS ALONE FAIL to attain glycemic goals, clinicians have numerous therapeutic options for advancing glucose control, the most common of which (currently) is addition of basal insulin (eg, insulin glargine, NPH, insulin detemir), followed by targeted prandial insulin for specific excessive post-meal glucose excursions (basal/prandial treatment). Rather than adding prandial insulin to glargine (in addition to oral agents), substituting multi-dose premix for basal/prandial insulin has some advocates, and has not yet been studied in a comparative trial.

Type 2 diabetics (n=374) unable to attain satisfactory control with oral agents plus basal insulin alone were randomly assigned to thrice daily premix insulin (Humalog Mix 50/50 or Humalog Mix 75/25) or glargine/lispro. At 24 weeks, the A1C attained was superior in the basal/prandial group to the premix group (6.78% vs 6.95%, $p = 0.021$). Since the trial was designed to test the non-inferiority of premix compared to basal/prandial with a prespecified margin of 0.3%, premix was NOT confirmed as non-inferior to basal/prandial. Similarly, the percent of patients achieving goal A1C < 7.0 was greater for basal/prandial than premix (69% vs 54%, $p = 0.009$); if the A1C target was the more strict <6.5%, basal/prandial still maintained advantage (50% achieved vs 35% on premix). ■

Rosenstock J, et al. Diabetes Care 2008;31:20-25.

A Relationship Between Linolenic Acid and Neuropathy in Diabetics

OVER 25% OF MID-LIFE DIABETICS have peripheral neuropathy (DPN), which is categorized as one of the microvascular consequences of diabetes based upon its putative origin in dysfunction of the vasonervorum. Good glycemic control has been found to forestall and prevent progression of neuropathy, but not reverse it. The search for etiologic factors in development of DPN has come to consider linolenic acid because of an identified relationship between high dietary linolenic acid intake and lesser macrovascular disease.

The NHANES (National Health and Nutrition Examination Survey) has periodically provided diverse US population data since 1971. In their most recent data set (1999-2004), an analysis of dietary linolenic acid in relation to DPN was examined.

Mean daily intake of linolenic acid (based upon 24-hour dietary recall report) was remarkably lower in persons with DPN (1.25 g/d) than diabetics without DPN (16.82 g/d). This is the first investigation to characterize the inverse association between linolenic acid and DPN, and as such requires replication and further elucidation of mechanisms by which linolenic acid might be protective. ■

Tao M, et al. Diabetes Care 2008;31(1):93-95.

In Future Issues: CT Scans and Radiation Exposure