Clinical Briefs in Primary Care™

The essential monthly primary care update

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Rethinking Postmenopausal HRT

Source: LaCroix AZ, et al. *JAMA* 2011; 305:1305-1314.

The final results of the women's Health Initiative trial (WHI) may not be the end of the story. Much-anticipated favorable cardiovascular outcomes from hormone replacement therapy (HRT) were conspicuously absent from the trial results at 7.1 years; when coupled with increases in stroke, thrombotic events, and breast cancer, most clinicians walked away from HRT. But the story doesn't end there.

Remember that the mean age of the WHI participants was 63 years; hence, most of the study subjects were more than a decade postmenopausal, not representative of the patients who typically seek relief of menopausal symptoms during the perimenopause and early menopausal years (usually ages 50-52 years).

The WHI included a large subset of hysterectomized women (n = 10,739) who received only estrogen therapy (i.e., no progestin). LaCroix et al report on extended post-trial follow-up of this population, adding another 5.8 years of observation to the original mean 5.9 years of the clinical trial.

At the 10.7 year mark, some of the initially described differences between estrogen and placebo were eradicated. Risk of coronary heart disease (CHD), deep vein thrombosis, stroke, hip fracture, and total mortality were not statistically significantly different in the two populations, even though initial results indicated some detrimental estrogen effects. At 10.7 years, there was a statistically significant 23% lower risk of breast cancer in women receiving estrogen replacement than placebo. As has been noted in previous recent publications about the WHI, younger women (age 50-59 years) had neutral or favorable outcomes for CHD, myocardial infarction, and total mortality, whereas older women incurred negative effects. Young (age 50-59 years) symptomatic women should have such considerations incorporated into decisions about HRT. ■

The Pistachio Diet for Erectile Dysfunction

Source: Aldemir M, et al. *Int J Impot Res* 2011;23:32-38.

Erectile dysfunction (ED) in mid-life males is recognized to stem most often from endothelial dysfunction, a commonplace consequence of dyslipidemia, diabetes, hypertension, or cigarette smoking. Pistachios have been shown to improve lipid fractions, but have not been studied in reference to functional improvement in endothelial function. To that end, Aldemir et al studied 17 men with established ED.

Study subjects ingested about 3½ ounces (570 kcal) of pistachios daily at lunch for 3 weeks. No other health interventions were used and subjects were asked to maintain similar exercise and other dietary patterns unchanged. At baseline and 3 weeks, the International Index of Erectile Function (IIEF) score and penile Doppler ultrasound were measured.

Compared to baseline, there was a statistically significant and clinically relevant increase in the IIEF score (from 36 at baseline to 54 at 3 weeks). Penile flow velocity improved by more than 20%. As had been confirmed in prior studies, favorable effects on total cholesterol, LDL, and HDL were seen.

The authors attributed the positive effects of pistachios potentially to antioxidant effects, as well as healthful lipid effects, the latter of which has previously been shown to promptly improve endothelial function. Because the studied "dose" of pistachios has substantial caloric impact (almost 600 calories), dietary restriction of other components for some patients might be necessary if they desire to add this amount of pistachios to their menu. ■

Vitamin D and Hypertension

Source: Bhandari SK, et al. *J Clin Hypertens* 2011;13:170-177.

Let's make this simple: vitamin D deficiency causes EVERYTHING. Well, at least that's the way things seem these days. In addition to the widespread awareness that insufficient vitamin D — as demonstrated by measurement of serum 25-hydroxy-vitamin D — is rampant, maladies from all spheres of medicine are increasingly recognized to be associated, to one degree or another, with vitamin D. Today, it is hypertension.

Bhandari et al begin their discussion of the relationship between vitamin D and hypertension (HTN) by pointing out that as many as 40% of U.S. adults are vitamin D deficient. Epidemiologic analyses suggest that all-cause mortality is lower in vitamin D supplemented

persons. Because vitamin D is involved with the renin-angiotensin-aldosterone system, it does not require a great stretch of the imagination to visualize a vitamin D-HTN linkage.

The data studied by the authors include 2,722 adult members of the Southern California Kaiser Permanente health care system. Rates of HTN were compared with quartiles of vitamin D. A linear and inverse relationship between vitamin D status and HTN was observed, such that individuals in the lowest vitamin D quartile were almost three times as likely to have HTN as those in the highest quartile.

Whether vitamin D supplementation could improve blood pressure or prevent development of HTN remains to be determined. In the meantime, add another item to the growing list of health issues in some way linked to vitamin D status. ■

Bromocriptine for Type 2 Diabetes

Source: DeFronzo RA. *Diabetes Care* 2011;34:789-794.

BROMOCRIPTINE (BRO) IS A NEW AND novel treatment for type 2 diabetes (DM2). In contrast to other classes of DM2 pharmacotherapy, which act at well-defined receptor sites to induce insulin secretion or improve insulin sensitivity, BRO works in a more global fashion by resetting levels of dopaminergic and sympathetic tone within the central nervous system (CNS). For example, elevation of hypothalamic dopamine levels reduces sympathetic nervous system activity resulting in improved glucose tolerance, reduced free fatty acids, and enhanced insulin sensitivity. The CNS effects can be harnessed by ingesting BRO in a rapid-release form (the form currently approved for DM2 treatment) in the morning, which is believed to reduce metabolic consequences of the morning dopamine decline often seen in diabetics.

A large (n = 3,070) 1-year randomized, placebo-controlled trial added BRO to various diabetes regimens, including diet, oral agents, and/or insulin. The BRO treatment group enjoyed a 40% reduction in the pre-specified cardiovascular endpoint (a composite of myocardial infarction, stroke, death, coronary revascularization, and hospitalization for angina or congestive heart failure). Although the mechanism by which BRO results in improved cardiovascular outcomes is uncertain, reductions in blood pressure and heart rate might be contributors. BRO is generally well tolerated and provides another category of treatment that may be used in combination with essentially any other diabetes medication. ■

Amitriptyline vs Duloxetine for Diabetic Peripheral Neuropathic Pain

Source: Kaur H, et al. *Diabetes Care* 2011;34:818-822.

DIABETIC PERIPHERAL NEUROPATHIC PAIN (DPNP) is challenging because not only does it induce a substantial pain burden, but also the pain is typically worse at night — resulting in sleep deprivation — and exacerbated by activity, compromising the ability for patients to perform the exercise that is so critical in weight maintenance. Although only two drugs have received specific FDA approval for management of DPNP (pregabalin, duloxetine), clinicians often use drugs off-label, including amitriptyline. Few head-to-head trials are available with which to compare various commonly used agents.

Kaur et al performed a double-blind crossover trial of amitriptyline (up to 50 mg/d) vs duloxetine (up to 60 mg/d) in 58 study subjects. The primary outcome was patient-assessed global efficacy at 6 weeks.

The outcomes with duloxetine and amitriptyline were essentially equivalent, and tolerability was also quite similar, although dry mouth was statistically significantly more common with amitriptyline. Comparable improvement in sleep was also seen with both medications. Since amitriptyline is available generically at a low price, it presents a viable therapeutic alternative for patients whose dry mouth is not a limiting adverse effect. ■

Testosterone Replacement in Diabetes and the Metabolic Syndrome

Source: Jones TH, et al. *Diabetes Care* 2011;34:828-837.

BOTH METABOLIC SYNDROME (MBS) AND type 2 diabetes (DM2) have been consistently found to be associated with low testosterone (TST) levels. Several new formulations of topical TST have become available in the last few years, simplifying treatment of hypogonadism. Jones et al studied the effects of TST 2% gel daily applications in hypogonadal men with MBS or DM2 treated for 1 year.

TST replacement produced numerous favorable effects in these hypogonadal men, including improvements in insulin resistance, a reduction in A1c, and lower LDL and lipoprotein A. Decreased libido and reduced sexual function are the most common presenting symptoms of hypogonadism, and numerous clinical trials have confirmed a prompt, sustained favorable response in these domains, which was similarly confirmed in this trial.

Tolerability of TST 2% gel was similar to placebo. When adverse effects did occur, more than 96% were considered mild or moderate. Cardiovascular (CV) events were seen more often in the placebo group, a reassuring finding since another trial published recently found a disarmingly marked increase in CV events in frail, senior men treated with TST.

In addition to improving target symptoms for which hypogonadal men seek relief, TST replacement can provide several other favorable metabolic effects in persons with DM2 or MBS. ■

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