Clinical Briefs in Primary Care™

The essential monthly primary care update

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Lifetime Risk of Developing COPD: A Longitudinal Population Study

Source: Gershon AS, et al. Lifetime risk of developing chronic obstructive pulmonary disease: A longitudinal population study. *Lancet* 2011;378:991-996.

WORLDWIDE, CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is the fourth most common cause of death, and is predicted to become the third most common cause in the near future, especially if smoking habits in populous nations like China — where more than half of adult men are currently smokers — continue on their same trajectory. According to Gershon et al, no prior publications have provided adequate insight into the lifetime risk of developing COPD. Hence, using health administrative data from the entire population of Ontario, Canada (n = approximately 13 million), they reported on a 14-year follow-up of persons who did *not* have COPD at baseline.

Based on the window of observation from 1996-2010, the population was divided categorically into: a) physician-diagnosed COPD, b) reached age 80 without a COPD diagnosis, or c) death. By age 80, more than one-fourth (28%) of persons free of COPD at baseline had been diagnosed with COPD by a physician. To put this into perspective, a new diagnosis of COPD was more likely than congestive heart failure, acute myocardial infarction, or even diabetes.

The authors mention that they have observed less public awareness of COPD than might be merited based on its epidemiological presence, and they encourage greater energies be invested in smoking cessation and public education about COPD. ■

The Burden of Painful Diabetic Peripheral Neuropathy

Source: Abbott CA, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011;34:2220-2224.

RECENTLY PUBLISHED TELEPHONE SURVEYS of large populations of diabetics indicate a low level of recognition of the diagnostic terminology "Diabetic Neuropathy," despite commonplace problematic symptoms consistent with this disorder. Diabetic peripheral neuropathy (DPN) and diabetic peripheral neuropathic pain (DPNP) are associated with major morbidities. For instance, the leading cause of amputation in diabetics is foot ulcer subsequent to impaired sensation in the feet from diabetic neuropathy. Similarly, DPNP is often worsened by activity, which tends to compromise exercise capacity and may also interrupt sleep.

The North-West Diabetes Foot Care Study screened 15,692 adult diabetics in northwest England. The presence of neuropathy was established using scoring systems as well as specific nerve function testing (vibration, pin-prick, temperature, and reflex testing). Screenings took place during routine annual evaluations by primary care clinicians.

Overall, one-third of study subjects experienced painful neuropathy. DPNP was twice as common in persons with type 2 diabetes than type 1. Women and persons of South Asian ethnicity were disproportionately affected. Based on these findings, clinicians might anticipate an important positive yield from routinely screening for symptoms of DPNP and signs of DPN. ■

Predictive Value of Postprandial Glucose for CV Events in Type 2 Diabetes

Source: Cavalot F, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: Lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011;34:2237-2243.

THE DECODE DATA (DIABETES EPIDEMIOLOGY Collaborative Analysis of Diagnostic Criteria in Europe) indicated that all-cause mortality, as well as cardiovascular (CV) events, were better predicted by postprandial glucose (PPG) than fasting blood glucose (FPG). Indeed, the DECODE data set indicates a linear rise in relative risk for mortality as one progresses from normoglycemia, to impaired glucose tolerance, to frank diabetes.

Although much of the literature is consistent in finding that PPG outperforms both FPG and A1C in predicting adverse CV events (and mortality), one criticism aimed at these data reminds us that PPG data were, for the most part, obtained from oral glucose tolerance testing (OGTT). Since only a small minority of patients outside clinical trials actually have OGTT performed, obtaining a PPG after actual meals might better reflect the pathophysiology occurring in long-term

management of diabetics.

Cavalot et al report on a 14-year follow-up of type 2 diabetes patients (n = 505) in whom A1C, FPG, and PPG (*not* obtained by OGTT) were measured at baseline, seeking to discern the relationship of each of these metrics with CV events and overall mortality.

For mortality as well as CV events, both A1C and PPG were strong predictors (especially post-lunch PPG). FPG was not a good predictor. It remains to be determined whether interventions specifically targeting PPG will provide meaningful benefit beyond simple traditional diabetes control. ■

Vitamin E and Prostate Cancer

Source: Klein EA, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;306:1549-1556.

Observational epidemiologic data had suggested that selenium, vitamin E, or both might reduce the incidence of prostate cancer (PCa). Based on this hypothesis, the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) was performed. The basic structure was a randomized, placebo-controlled trial of vitamin E 400 IU/d (VitE), selenium 200 mcg/d (SEL), or both in 35,533 men. Seven years after enrollment, the trial was stopped because of a lack of any demonstrated benefit along with futility analysis indicating no potential of future benefit. That was in 2008.

This report extends follow-up of the same population through 2011. At this point, a statistically significant *increased* risk of prostate cancer was seen in men taking VitE (17% increase). While the numbers for SEL as well as SEL plus VitE trended toward worse outcomes, they were not statistically significant.

Why VitE might produce an increased risk for PCa is unclear: There was, for instance, no measurable effect of VitE on PSA. Although many clinicians have opted to be essentially silent in discussions of vitamin supplements with patients — since, after all, vitE was presumed to be innocuous — these data suggest consideration of intervention to discourage VitE in healthy men. Although the data were insufficient to definitively indict selenium, there is no support for endorsing it either. ■

Is There a Relationship Between Insulin Glargine and Cancer?

Source: Morden NE, et al. Further exploration of the relationship between insulin glargine and incident cancer: A retrospective cohort study of older Medicare patients. *Diabetes Care* 2011;34:1965-1971.

Recent retrospective studies in Europe have created concern because of an observed increased risk of cancer (hazard ratio = 1.55) in users of insulin glargine (GLAR) compared to nonusers. Similarly, increased risk of breast cancer in GLAR users was reported in two other analyses (hazard ratio 1.99-3.9). These reports, in addition to the limitations of their retrospective design, also had limitations such as failure to adjust for potential confounders such as BMI, GLAR dose, the impact of socioeconomic selection bias, and the relatively short periods of observation (6 years or less).

To remedy some of the limitations of early reports, the authors reviewed a Medicare database of more than 81,000 diabetics, including a subpopulation of 16,945 on GLAR and 49,455 on insulins other than GLAR. After adjustment for recognized confounders, there was no association seen between GLAR and any cancer. Indeed, combination insulin regimens were associated with increased risk of breast cancer, an association not previously consistently identified.

The results of this large data set should be generally reassuring about the safety profile of GLAR in reference to cancer of any type. The association of breast cancer with combination insulin regimens noted here should not be considered definitive because various reports have come to conflicting conclusions. ■

Saw Palmetto and BPH: *Not*

Source: Barry MJ, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA* 2011;306:1344-1351.

Although benign prostatic hyperplasia (BPH) and its consequences are rarely a mortal concern, the quality-of-life impact of LUTS (Lower Urinary Tract Symptoms) associated with BPH is often substantial. Antihypertensive alpha blockers (e.g., doxazosin, terazosin), site-selective alpha blockers (e.g., alfuzosin, tamsulosin), and alpha-reductase inhibitors (e.g., dutasteride, finasteride) have each been shown — either alone or in combination (i.e., alpha blockers + alpha reductase inhibitors) to improve LUTS. The latter have even been shown to reduce the need for surgery and the incidence of acute urinary retention in BPH study subjects.

Despite the well-demonstrated efficacy of proprietary agents, many BPH patients opt for "natural" treatments, such as saw palmetto (SWP). An early Cochrane review (2002) of SWP was generally supportive; less positivity was reflected in the 2009 Cochrane review, because more recent, rigorous trials found lesser benefit. Most trials utilized SWP 160 mg b.i.d. Is it possible that *more* SWP might gain greater therapeutic efficacy?

Barry et al performed a randomized, double-blind trial of higher-dose SWP, including doses up to 960 mg/d. Men with BPH (n = 369) were followed for 72 weeks. At the conclusion of the trial, no beneficial effects on LUTS were seen, despite the higher dose. No serious adverse effects attributable to SWP were seen. Based on these data, SWP is not beneficial for men with BPH. ■

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