

Clinical Briefs in **Primary Care**™

The essential monthly primary care update

By Louis Kuritzky, MD

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COPD in Never Smokers

Source: Lamprecht B, et al. *Chest* 2011; 139:752-763.

UNLESS THERE IS ANOTHER OVERT CAUSE, such as occupational exposure to toxic inhalants, we generally expect chronic obstructive pulmonary disease (COPD) to be secondary to cigarette smoking. The pulmonology literature consistently suggests that a substantial minority — at least 20% — is NOT related to cigarette smoking. This multinational survey by Lamprecht et al provides a fresh appraisal of the burden of COPD unrelated to smoking.

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines were used to define COPD through spirometry. Primary cigarette smoking, exposure to secondary smoke, occupational exposure, and biomass exposure (for instance, cooking or home heating using wood, coal, dung, or crop residue) were all queried among 10,000 subjects from 14 countries.

Of the 4291 never smokers, 12.2% fulfilled GOLD criteria for COPD. Of all persons ultimately defined as meeting COPD criteria, just over one-fourth were never smokers. Women were disproportionately represented in the group of persons with moderate-severe COPD. It has been suggested that women may have greater susceptibility both to tobacco smoke as well as other potentially toxic inhalants.

COPD is now the third most common cause of death in America. Pulmonologists have suggested that COPD remains underdiagnosed. Based on these results, the authors suggest that symptomatic persons, even if never smokers, should be screened for COPD. ■

Early Prostate Cancer: Prostatectomy vs Watchful Waiting

Source: Bill-Axelson A, et al. *N Engl J Med* 2011;364:1708-1717.

THE MANAGEMENT OF EARLY PROSTATE CANCER (PCA) remains controversial. Although surgical and radiation interventions offer the opportunity for cure, many more men with early PCA die with the disease than from it. Were definitive interventions without risk, there likely would be little discussion about whether to intervene; however, because the potential consequences of intervention are significant (e.g., incontinence, erectile dysfunction), clarification of the risk:benefit ratio is critical.

A randomized multinational study of subjects from Sweden, Finland, and Iceland (n = 695) randomized men < 75 years of age with localized, moderately well to well-differentiated prostate cancer to either radical prostatectomy or watchful waiting. Men were followed for 12.8 years.

At 12.8 years, all-cause mortality was statistically significantly less in the surgery group (166/347) than the watchful waiting group (201/348). Similarly, PCA-related death was superior in the surgically treated group (14.6% vs 20.7%). Benefits were clear from men < 65 years of age, but only a trend toward benefit (results not statistically significant) could be determined from the data in older men, possibly because of the smaller number of men in this age group.

Adverse effects of surgery were substantial. For instance, at 1 year, 32% of men had incontinence and 58% had impotence. Younger men with early PCA appear to enjoy mortality benefit from

surgical intervention, though at a substantial adverse event cost. Competing causes of death in older men diminish the relative benefits of surgery. ■

Dietary Vitamin D and Incident Diabetes

Source: Gagnon C, et al. *Diabetes Care* 2011;34:1133-1138.

THE BETA CELLS OF THE PANCREAS POSSESS a vitamin D receptor, so perhaps we should not be surprised that vitamin D might be associated with diabetes (DM). Preliminary evidence has suggested that dietary vitamin D (VTD) might be associated with risk for DM, but prior to this report, no large population study has provided sufficient information to be definitive.

Gagnon et al researched subjects involved in the AusDiab studies, which included 11,247 noninstitutionalized adults free of DM at baseline who underwent a 75 g oral glucose tolerance test (GTT) at baseline. Five years later about half (6537) of these had a repeat GTT, of which 80% were still not diabetic.

The investigators found a linear relationship between reported dietary VTD and incident DM over a 5-year interval: for every 25 nmol/L increase in VTD, there was a 24% reduced risk of DM. Also studied in this same data set was calcium intake, which did not correlate with incident DM. Subjects in the top quartile of VTD intake enjoyed a 44% risk reduction for incident DM.

Because these are observational data, causation cannot be established. Prospective, randomized, placebo-controlled trials of VTD supplementation will be necessary to confirm the preventive capacity of VTD. ■

Functional Cobalamin Deficiency in Diabetes

Source: Solomon LR. *Diabetes Care* 2011;34:1077-1080.

IT HAS BEEN SUGGESTED THAT AS MANY AS 30% of senior citizens have so-called functional cobalamin deficiency (FCD), defined as the presence of elevated metabolites such as methylmalonic acid in the face of ostensibly normal cobalamin levels. Since methylmalonic acid should accumulate primarily in the circumstance of vitamin B12 insufficiency, there appears to be some functional deficiency in cobalamin, manifested as increased levels of methylmalonic acid.

The intersection of diabetes with FCD occurs because previous trials have noted that diabetics comprise up to one-third of subjects experiencing improvements in neuropathic signs with vitamin B12 supplementation, and the vast majority of these subjects (88%) did not have decreased vitamin B12 levels.

To better define the epidemiologic profile of FCD, a retrospective review of patients evaluated for cobalamin deficiency from 1993-2005 characterized levels of cobalamin in relation to methylmalonic acid. Because renal insufficiency is associated with increases in methylmalonic acid, creatinine > 1.4 mg/dL was an exclusion criterion.

Among nondiabetics there was an inverse relationship between methylmalonic acid and cobalamin. Among diabetics, how-

ever, increasing cobalamin levels were not associated with decreasing methylmalonic acid, suggesting that there was a relative cobalamin resistance.

Equally noteworthy, neuropathy was much more frequent in persons with elevated methylmalonic acid than without (62% vs 18%) and more than 85% of persons treated with pharmacologic doses of cobalamin experienced improvement in neuropathy.

There is substantial controversy over the existence of functional cobalamin deficiency. Considering that cobalamin supplementation has no known important toxicity, clinicians may wish to re-examine the issue of cobalamin treatment for diabetic subjects with elevated levels of methylmalonic acid, even in the face of normal cobalamin levels. ■

Should Leukotriene Antagonists Have Higher Priority for Asthma Control?

Source: Price D, et al. *N Eng J Med* 2011;364:1695-1707.

CURRENT ASTHMA GUIDELINES SUGGEST that once an asthma patient has progressed to the stage of persistent asthma (even mild-persistent asthma), inhaled corticosteroids (ICS) should be the preferred initial "controller" (maintenance) medication. Nonetheless, comparator trials of leukotriene inhibitors (LKT) with ICS have produced inconsistent findings, sometimes indicating superiority of ICS, but other times suggesting equal efficacy of the two classes. Because concerns about adverse effects of ICS in obstructive airways diseases have persisted for several decades, the absence of similar concerns with LKT agents promotes consideration of how to maximize their positive potential.

Two trials comprise the data reported in this publication. In the first, persons initiating controller therapy for persistent asthma (n = 306) were randomized to either ICS or LKT. In the second trial, asthma subjects who had already received ICS for controller medication but who required advancement of pharmacotherapy (n = 352) were randomized to either LKT or long-acting beta agonist (LABA). The primary outcome was the score on the Mini Asthma Quality of Life Questionnaire at 2 months. Secondary outcomes included the same questionnaire results at 2 years and fre-

quency of asthma exacerbations.

At 2 months, the LKT proved equivalent to ICS as initial therapy, and equivalent to LABA as add-on treatment. At 2 years, although not able to achieve the statistical threshold defining equivalence, the outcomes were very similar. There was no difference in the frequency of exacerbations between LKT and ICS or between LKT and LABA when added to ICS. There was no placebo control in this trial, and the trial was open label. Nevertheless, these data suggest that in a "real world" setting, the efficacy of LKT in asthma may have been underestimated. ■

Selenium Impacts Orbitopathy in Graves Disease

Source: Krassas GE, et al. *N Eng J Med* 2011;364:1920-1931.

OCULAR ABNORMALITIES ASSOCIATED WITH Graves disease are sometimes called Graves' orbitopathy (GORB) and occur in as many as half of Graves' disease cases. Treatments for GORB include glucocorticoids and irradiation, but are generally reserved for moderately severe disease. Mild GORB has been shown to spontaneously regress (20%), remain stable/unchanging (65%), or advance (15%). Hence, a safe intervention to prevent advancement of GORB would be desirable. The antioxidant effects of selenium led to consideration of its potential favorable impact upon GORB.

This controlled trial randomized patients (n = 107) to selenium sulfide 100 mcg twice daily or placebo for 6 months. GORB evaluation was done at baseline, 3, 6, and 12 months. The primary outcome was the percentage of patients improving from baseline. The study hypothesis was that active treatment would improve the number of persons with GORB regression by 25%: from 20% (as seen in naturalistic follow-up of untreated GORB) to 45%.

By 6 months, there was a statistically significant improved quality of life and regression of GORB, which was reconfirmed at 12 months. There were no serious adverse effects seen with selenium.

Although it would have been nice to have seen selenium levels before and after treatment, and hopefully a correlation between selenium repletion and outcomes, these preliminary data are still quite supportive of a

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Customer Service: 1-800-688-2421

E-Mail Address: neill.kimball@ahcmedia.com

World Wide Web: www.ahcmedia.com

Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

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