

Clinical Briefs in Primary Care

By Louis Kuritzky, MD

Evidence-based updates in primary care medicine

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Glucose Variability in T2DM: Ready for Prime Time?

SOURCE: Kovatchev B, Cobelli C. *Diabetes Care* 2016;39:502-510.

The benefits of glycemic control in type 2 diabetes (T2DM) include improved microvascular status (retinopathy, neuropathy, nephropathy), and better quality of life. Striving for progressively better control of hyperglycemia is typically associated with an increased incidence of hypoglycemia, consequences of which can range from transient unpleasant central nervous system dysfunctions and signs of autonomic activation to coma and death.

While A1c is an accurate measure of mean glucose levels, two individuals with the same A1c level can present markedly different excursions of glucose above and below the mean, which generates A1c. Typically, higher glucose variability above and below the mean reflects more episodes of greater hyperglycemia as well as hypoglycemia, which may not be readily discerned through just examining A1c. Continuous glucose monitoring, as well as frequent self-monitoring of blood glucose, have created a window of observation to detect glucose variability.

What's the practical yield of attending to glucose variability? There is still some disagreement about the best way to measure variability, since hyperglycemic excursions typically are much less concerning than similar reductions toward hypoglycemia, so it may be necessary to use separate metrics for hypo- vs. hyperglycemic variability. Additionally, computations to assess glucose variability are not paper-and-pencil simple — they require computational

tools. However, it has been shown that, as an example, at the same A1c level glucose variability was substantially less in patients taking oral agents who added a GLP1-RA (e.g., exenatide) vs. insulin glargine. While not yet a tool for routine practice, analysis of glucose variability appears to hold promise for the future. ■

Improvements in Pain and Physical Function After Bariatric Surgery

SOURCE: King WC, Chen JY, Belle SH, et al. *JAMA* 2016;315:1362-1371.

The metabolic benefits of bariatric surgery are prompt, significant, and — for the most part — durable. Many patients who suffer from severe obesity also experience joint pain (especially knee and hip) and limited mobility. What kind of effect does bariatric surgery have on those endpoints?

King et al reported on outcomes among patients with severe obesity (median body mass index = 49.5) who underwent bariatric surgery (n = 2,221). The outcomes of interest were bodily pain and physical function, as measured by SF-36. To be considered “improved,” patients had to meet the threshold for minimal meaningful increment of change, rather than just achieve statistical significance alone.

At one year, the majority of surgical subjects demonstrated clinically meaningful improvements in pain and physical function. Specifically addressing those already experiencing disability due to knee (n = 633) or hip (n = 500) pain at baseline, > 75% of each group reported symptomatic

improvement at one year, which was durable through three years of observation.

In addition to the favorable metabolic changes (e.g., remission of diabetes, prevention of diabetes) associated with bariatric surgery, meaningful improvements in physical function and disability due to joint pain occur promptly and are durable through at least three years of follow-up. ■

Two Thumbs Down for COPD Screening

SOURCE: U.S. Preventive Services Task Force. *JAMA* 2016;315:1372-1377.

Since none of the currently available pharmacologic treatments for COPD can be considered “disease modifying” (that is, alters the course of progression or reduces mortality), even if we were to identify COPD early, why would we have any confidence that treatment would be beneficial? Despite numerous clinical trials demonstrating improvements in lung function, activity, frequency of exacerbations, and symptoms in COPD patients, none of the medications have been able to achieve the lofty threshold of disease modifying. Only smoking cessation and oxygen at late-stage disease have been found to be disease modifying.

Upon review of the currently available evidence, the U.S. Preventive Services Task Force (USPSTF) assigned a level “D” recommendation to the issue of screening asymptomatic adults for COPD, which means, “the USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”

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Within their Recommendation Statement, the USPSTF included recognition of one potentially valuable role of screening with spirometry: enhancing quit rates among smokers. But even then, results of clinical trials are mixed. Only one study that presented pulmonary status using the technique of “lung age” had an effect on smoking cessation rates; other studies presenting spirometry results in “traditional methodology” did not improve smoking cessation outcomes.

These USPSTF recommendations should not be misconstrued to reflect on the utility of spirometry for symptomatic individuals. ■

Subclinical Thyroid Disease Associated with Increased Mortality in Seniors

SOURCE: Grossman A, Weiss A, Koren-Morag N, et al. *Am J Med* 2016;129:423-430.

Subclinical thyroid disease is defined as altered thyroid stimulating hormone (TSH) level in the presence of normal thyroid hormone (T4, T3) levels. Hence subclinical hypothyroidism exists when TSH levels are elevated but T4 is normal, and subclinical hyperthyroidism exists when TSH levels are reduced, but T3 and

T4 levels are normal. Since a substantial number of cases of overt hyperthyroidism and overt hypothyroidism are immediately preceded by a period of subclinical status, it probably should not be surprising that subclinical thyroid disease status (both hyper and hypo) is associated with mortality in elders.

Grossman et al performed a retrospective analysis on patients > 65 years of age (n = 17,440), comprised of individuals with normal thyroid status (n = 14,946), subclinical hyperthyroidism (n = 538), and subclinical hypothyroidism (n = 1,956) who were followed for as long as 10 years.

Both subclinical hypo- and hyperthyroidism were associated with increased risk for mortality (hazard ratio = 1.53 and 2.33, respectively). In the population of subjects with subclinical hypothyroidism, a TSH > 6.35 mIU/L was the threshold for increasing mortality risk. Subclinical hyperthyroidism has been associated with increased risk for atrial fibrillation, so the increased mortality risk in this population is perhaps less surprising. ■

An Infectious Disease Causes Pathological Aggression?

SOURCE: Coccaro EF, Lee R, Groer MW, et al. *J Clin Psychiatry* 2016;77:334-341.

Many have followed an evolution of medical disorders surprisingly linked to infectious diseases: cervical cancer (Human papillomavirus infection), gastric and peptic ulcer disease (*Helicobacter pylori*), and even obesity (adenovirus 36). *Toxoplasma gondii* (TXG) is a highly prevalent protozoan reportedly infecting, albeit usually asymptotically, as many as one-third of U.S. adults. Humans can acquire TXG from household cat feces and less commonly from undercooked meat infected with TXG. In immunocompetent humans, TXG lives in the central nervous system within neurons and glial cells and is generally asymptomatic, although associations between latent TXG and schizophrenia, bipolar disease, and personality disorders have been demonstrated.

Coccaro et al performed sero-analyses on 358 adults comprised of approximately three equally sized groups: healthy controls, psychiatric controls without noteworthy aggression issues, and psychiatric patients with intermittent explosive disorder. A TXG IgG antibody titer greater than 12 IU was regarded as seropositive.

Positive TXG sero-status was statistically

significantly associated with aggression. Prevalence of TXG seropositivity ranged from 9.1% in healthy controls to 16.7% in psychiatric controls (without aggression issues) to 21.8% in subjects with intermittent explosive disorder. These preliminary results do not include any advice about if, how, or when TXG treatment should be considered. ■

Pioglitazone and Secondary CV Prevention

SOURCE: Kernan WN, Viscoli CM, Furie KL, et al. *N Engl J Med* 2016;374:1321-1331.

In addition to “traditional” risk factors for cardiovascular (CV) events (e.g., hyperlipidemia, hypertension, cigarette smoking), it has not gone unnoticed that insulin resistance, even in the absence of frank diabetes, also is associated with stroke and myocardial infarction (MI). Might a pharmacologic agent that improves insulin resistance be effective in secondary prevention of CV events?

Kernan et al performed a randomized, double-blind, placebo-controlled trial of adults who had sustained a stroke or transient ischemic attack (n = 3,876) to compare pioglitazone, an agent that improves insulin sensitivity, to placebo. Diabetic patients were excluded; rather, inclusion criteria required that patients demonstrate insulin resistance (as measured by the HOMA-IR metric), but did not meet criteria for diabetes. The primary outcome was fatal or nonfatal stroke or MI.

At 4.8 years, subjects who had been treated with pioglitazone enjoyed a 24% relative risk reduction in the primary endpoint (9% vs. 11.8%). Additionally, pioglitazone served well as a tool to prevent progression to diabetes by reducing incident diabetes more than 50% (3.8% vs. 7.7%). There was a trend toward lower mortality in the pioglitazone group that did not achieve statistical significance.

Before making an abrupt practice change based on this study, it is important to note that the incidence of fracture requiring surgery or hospitalization statistically significantly increased in the pioglitazone treatment arm (5.1% vs. 3.2%). Hence, the absolute reduction in CV events (almost 3%) is nearly offset by the increase in fractures (nearly 2%). Arguably, elimination of a major CV event substantially outweighs a new bone event, but clinicians should consider such adverse events in their therapeutic decision process, especially in patients acknowledged to be at high risk for fracture. ■

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SUBSCRIBER INFORMATION

Customer Service: (800) 688-2421

Email Address: Jonathan.Springston@AHCMedia.com

Website: AHCMedia.com

Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

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