Clinical Briefs in
Primary Care

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Evidence-based updates in primary care medicine

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Long-term Outcomes for Obesity

SOURCE: Jakobsen GS, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. *JAMA* 2018;319:291-301.

For most patients, managing obesity is a long-term endeavor. Recent proliferation of oral and parenteral anti-obesity agents has increased the number of pharmacologic treatments. Still, long-term weight reduction achieved with such treatments, in combination with lifestyle interventions, is modest (typically, 5-10% body weight decline). Additionally, pharmacologic treatments are not disease-modifying; that is, after medication cessation, weight regain occurs consistently and predictably.

Obesity surgery produces prompt and highly effective metabolic changes that favorably affect prevalent and incident diabetes and hypertension. But do these results last? To answer that question, Jakobsen et al reported on a 10-year follow-up of patients with obesity who were offered their choice of surgical or intensive medical treatment (n = 1,888) at a publicly funded tertiary care obesity center in Norway.

Outcomes differences between the groups were dramatic. Subjects who chose surgical treatment were twice as likely to go into hypertension remission, four times less likely to develop new onset hypertension, and four times more likely to experience remission of diabetes than medically treated subjects. Although surgical intervention was not without adverse effects, including a difficult-to-explain modest increased incidence of depression, metabolic benefits were consistent and enduring. The evidence of the advantages of bariatric surgery over medical management continues to accrue. ■

Biomarkers for Tight Control of Crohn's Disease

SOURCE: Colombel JF, et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. *Lancet* 2018;390:2779-2789.

Colombel et al investigated the effect of including biomarkers, in addition to clinical signs and symptoms, for management of Crohn's disease. This multinational study enrolled patients with Crohn's disease into an open-label study with two treatment arms: tight control (i.e., intensification of treatment based on clinical signs and symptoms, as well as optimization based on levels of C-reactive protein and fecal calprotectin) vs. clinical management (treatment intensification based on symptoms/signs of disease activity alone). Main treatments included prednisone, adalimumab, and azathioprine. The primary endpoint was mucosal healing with absence of deep ulcers at 48 weeks.

A statistically significantly greater proportion of subjects in the tight control group achieved the primary endpoint than the clinical management group (46% vs. 30%), while adverse effects and dropouts were similar between the two groups. The authors suggested that treatment escalation based on the combination of clinical symptoms with biomarkers produces more favorable outcomes. ■

Postprandial Glucose Excursions in Type 2 Diabetes

SOURCE: Yacoub T. Impact of improving postprandial glycemic control with intensifying insulin therapy in type 2 diabetes. *Postgrad Med* 2017;129:791-800.

One commonly advocated method for approaching correction of hyperglycemia in type 2 diabetes is "fix the fasting first." Basal insulins have been used commonly to fix fasting glucose, but even with sensible combinations of insulin and oral agents, as many as 40% or more of patients will need to address postprandial glucose excursions (PPG) to attain desirable A1c goals.

In support of maintenance of PPG, epidemiologic data point to an association between PPG and cardiovascular disease risk. Whether management of PPG ameliorates consequences (independently from overall glucose control, especially fasting glucose) has been more difficult to confirm. Repaglinide is a rapid-acting oral agent producing prompt but short-lived insulin secretion from beta cells. Although the receptor site for repaglinide is the same as that for sulfonylureas (e.g., glipizide, glimepiride), it is in a distinct pharmacologic category because it differs structurally from sulfonylureas and lacks a sulfonamide group characteristic of sulfonylureas.

In a clinical trial comparing repaglinide with glyburide, PPG was reduced more with the former; repaglinide also was associated with greater carotid intima media thickness regression. When control of fasting glucose has been achieved

but excessive PPG excursions remain, therapeutic choices include adding prandial insulin, alpha-glucosidase inhibitors (e.g., acarbose), or adding glucagon-like peptide-1 receptor agonists (e.g., liraglutide, exenatide). Currently, it is unclear what the preferred method of PPG control should be, but the most recent American Diabetes Association 2018 guidelines suggest that for persons with established cardiovascular disease who have not attained glucose goals, incorporation of agents that have shown cardiovascular risk reduction (i.e., canagliflozin, empagliflozin, liraglutide) should be a priority. ■

Cardiovascular Benefits of Pharmacotherapies for Type 2 Diabetes

SOURCE: Yandrapalli S, et al. Cardiovascular benefits and safety of non-insulin medications used in the treatment of type 2 diabetes mellitus. *Postgrad Med* 2017;129:811-821.

The primary goals of diabetes management are reductions in microvascular endpoints (retinopathy, neuropathy, nephropathy), macrovascular endpoints (myocardial infarction, stroke), and improved quality of life (less dry mouth, urinary frequency, visual disturbance). In the most recent decade, the FDA has mandated that new pharmacologic entities for management of glucose in type 2 diabetes (T2DM) establish cardiovascular (CV) safety with a substantial clinical trial. As a result, there are now several agents that have shown not only CV safety in T2DM, but also actual reductions in CV endpoints.

The three agents with FDA labeling for CV risk reduction based on their successful clinical trials are empagliflozin (EMPA-REG), canagliflozin (CANVAS), and liraglutide (LEADER). Another glucagon-like peptide-1 receptor agonist, semaglutide, has been approved for treatment of T2DM. It demonstrated CV risk reduction in a recent clinical trial (SUSTAIN), but does not yet carry FDA labeling for CV risk reduction.

The most recent American Diabetes Association 2018 guidance for pharmacotherapy of T2DM suggests that for patients with existing CV disease who are uncontrolled on metformin and lifestyle, consideration should be given to prioritizing agents demonstrated to provide CV risk reduction (empagliflozin, liraglutide, and canagliflozin). ■

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Osteoblast Modulation in Osteoporosis Treatment

SOURCE: Corrado A, et al. Osteoblast as a target of anti-osteoporotic treatment. *Postgrad Med* 2017;129:858-865.

In healthy bones, osteoclast activity is balanced with osteoblast activity to produce a continuing stream of freshly created bone by degradation of aging bone and replacement with new bone. After attainment of the peak level of mature bone in early adulthood, osteoclast activity modestly exceeds osteoblast activity, leading to a gradual decline in bone mineral density that we call age-related bone loss to distinguish it from the more rapid bone loss seen at menopause (regardless of age) due to estrogen loss that characteristically outpaces simple age-related bone loss.

Most pharmacologic interventions currently in use for treatment or prevention of osteoporosis rely on osteoclast inhibition to enhance (or at least maintain) bone mineral density. In contrast, teriparatide primarily works by stimulation of osteoblasts. Estrogen also produces some positive activity on osteoblasts, such as inhibition of osteoblast apoptosis. Finally, even though the primary mechanism of bisphosphonates is inhibition of osteoclastic activity, even this pharmacologic class produces some favorable effects on osteoblasts.

One additional class of pharmacologic agent has shown promising effects: The anti-sclerostin antibody agent romosozumab provides both stimulation to osteoblasts and diminution of osteoclast activity. This agent is pending FDA approval. ■

The Vagaries of Reported Penicillin Allergy

SOURCE: Sundquist BK, et al. Proactive penicillin allergy testing in primary care patients labeled as allergic: Outcomes and barriers. *Postgrad Med* 2017;129:915-920.

I am allergic to penicillin, or at least that's what I say in healthcare settings when someone asks. My designation as penicillin allergic occurred around age 5 when I developed a rash after a shot of penicillin. The malady I was suffering was called "a respiratory infection," with the subsequent all-encompassing remedy supplied: a shot of penicillin (at least that's how it was in 1951). I am told that within the next day or two I developed a rash, and was told to eschew penicillin.

But was I really allergic? Certainly, there are many commonplace viral upper respiratory illnesses afflicting youngsters that can manifest a rash. Subsequently, I have received cephalosporins uneventfully. The literature says that > 90% of patients who report a history of penicillin allergy can tolerate penicillin. Unstimulated penicillin sensitivity wanes over time: By age 10 years, 80% of allergic subjects are no longer allergic.

Sundquist et al recruited patients with a history of penicillin allergy. Skin testing in 37 subjects (prick testing and intradermal testing) identified *none* as allergic; subsequent oral challenge also demonstrated *no* positive results. The authors suggested that good antibiotic stewardship supports consideration of clarification of whether patients who report penicillin allergy are allergic. Numerous infectious diseases are best served by penicillin treatment for the sake of cost considerations, specificity, and antibiotic stewardship. ■