Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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Does It Really Make a Difference What Weight-Reduction Diet You Choose?

Source: Johnston BC, et al. *JAMA* 2014; 312:923-933.

Since two-thirds of American adults are currently overweight or obese, we would all like to be able to help patients choose the "best" diet. The list of choices and categories is lengthy, with vocal advocates for the Atkins diet, the Zone diet, South Beach diet, Jenny Craig, Ornish, etc. Of course, were any of these diets sufficiently effective and easily adopted that they could gain widespread advocacy, we wouldn't be faced with such an obesity epidemic in the first place! So, apparently there is no "simple answer." Among the choices we have, then, which one might be the best?

Johnston et al performed a meta-analysis of weight loss trials (n = 48 trials and 7286 subjects), including the above-mentioned diets. Diets were categorized further as low carbohydrate or low fat.

Although there were measurable *statistical* differences between diets, they were of dubious clinical significance. For instance, at 12-month follow-up, low-carbohydrate diets were associated with a mean weight reduction of 7.99 kg vs 7.27 kg on low-fat diets. Within-group diet differences — e.g., comparing Atkins and Zone diets, both of which are categorized as low carbohydrate — favored Atkins, but these differences were also very small (< 2 kg at 6 months).

Because of the modest outcome differences between diets, the authors conclude that whatever diet the patient can best adhere to should be recommended. ■

Treatment of Depression with Botulinum Toxin

Source: Magid M, et al. *J Clin Psychiatry* 2014;75:837-844.

The need for additional treatments for depression stems from the observation that only a minority of patients achieve full remission on currently available antidepressant medications, each of which has its own adverse effect profile. In the 1963 musical "Bye Bye Birdie," Dick van Dyke sang the song "Put On a Happy Face" to Janet Leigh. Having followed Dick's advice, Janet undergoes a prompt and readily visible transformation of her energy and mood. Well, maybe there was some substance to that advice, as suggested by this clinical trial of botulinum toxin (B-TOX).

The Facial Feedback Hypothesis suggests that when one volitionally produces a particular facial expression (e.g., frowning, smiling), concordant emotions are experienced, perhaps through some CNS feedback mechanism. So, might elimination of frown muscle tone with B-TOX improve mood?

Magid et al randomized 30 patients with depression to B-TOX vs placebo administered at baseline in the facial glabellar region frown musculature. Depression scores were measured over 24 weeks post-injection.

B-TOX was associated with a statistically significant reduction in depression scores, which persisted throughout the 24-week interval, even though the cosmetic effects on the facial frown musculature dissipated by 12-16 weeks. Reductions in depression scores on the Beck Depression Inventory were impressive: more than one-third of B-TOX recipients achieved at least a 50% reduction in depression scores. B-TOX appears to be a prompt and effective treatment for depression. ■

Adenoma Removal and Long-term Colorectal Cancer Mortality

Source: Loberg M, et al. *N Engl J Med* 2014;371:799-807.

Compared to other preventive health screening interventions, adherence to colonoscopy (COL) recommendations is substantially less than that of other interventions. The payoff of reduced risk of colon cancer seems insufficient inducement for patients to undergo the procedural preparation and intervention for many of our patients. Just how big is the payoff?

Loberg investigated the impact on colon cancer mortality of adenoma removal during COL screening. They compared the colon cancer mortality over a 14-year interval (median follow-up, 7.7 years) for persons who had undergone colonoscopic adenoma removal with the colon cancer mortality in the entire adult population of Norway. The primary outcome of the study was the rate of colon cancer mortality as assessed by the Stratified Mortality Ratio (SMR) — the rate of colon cancer deaths in persons with adenomas removed vs the colon cancer death rate in the general adult population.

Based on 383 colon cancer deaths

among 40,826 adenoma patients, compared to 398 colon cancer deaths in the general population, the overall SMR (including all classes of adenomas excised) demonstrated a trend toward lower colon cancer mortality (SMR, 0.96; 95% confidence interval, 0.87-1.06). ■

Hepatitis C Treatment: Just How Much is it Worth to Cure a Dreadful Disease?

Source: Brennan T, Shrank W. *JAMA* 2014;312:593-594.

The trouble with the expense of treating hepatitis C virus (HCV) infections is that very few patients are acutely "choking" on it, since the largest pool of HCV patients are asymptomatic. Progression to end-stage liver disease, liver transplantation, and hepatocellular carcinoma — the three most dreaded HCV consequences — may seem distant to the asymptomatic or even modestly symptomatic patient. The current costs of some HCV regimens appear, at least at first glance, extraordinary. For instance, once-daily oral sofosbuvir, one of the most highly effective HCV treatments, is a startling $84,000 for a standard 12-week course ($1000 per pill)!

Although neither the public nor clinicians are readily aware of the per-tablet costs of actually creating a new therapeutic entity, it is perhaps noteworthy that the initial purchase of the company that first developed sofosbuvir was $11 billion. This number does not include any of the costs for subsequent manufacture and marketing, and of course it will take many, many courses of sofosbuvir to recoup even these initial expenses. On the other hand, if every HCV patient in the United States were to enjoy a curative treatment course of sofosbuvir at the standard price, that could generate as much as $250 billion.

Certainly the costs of treatment for liver transplantation, end-stage liver disease, and hepatocellular carcinoma would readily eclipse even this apparently extravagant tariff for sofosbuvir and some other agents like it, such that in the long-term perspective, it becomes "pay me a lot now or pay a lot more later." In any case, many voices are calling for the industry to be economically and socially responsible stewards of the treatments they offer. ■

Obesity and Cancer

Source: Bhaskaran K, et al. *Lancet* 2014; 384:755-765.

The link between obesity and adverse cardiovascular outcomes can be fairly directly attributed to readily visible obesity comorbidities such as increases in blood pressure, dyslipidemia, and sedentary lifestyle. But what about cancer?

According to a recent analysis in *Lancet* based on records from primary care records in the United Kingdom (n = 5.24 million), there is a meaningful relationship between increasing body mass index (BMI) and cancer.

For instance, for every 5 kg/m^2 increase in BMI, statistically significant hazard ratios increased for cancers of the uterus (HR = 1.62), gallbladder (HR = 1.31), kidney (HR = 1.25), cervix (HR = 1.10), and thyroid (HR = 1.09). Not all cancer risks were magnified by increasing BMI. For instance, prostate cancer and premenopausal breast cancer were inversely associated with BMI.

According to this analysis, as many as 41% of uterine cancers and 10% gallbladder, kidney, liver, and colon cancers are related to being overweight in the United Kingdom. The mechanism(s) by which increasing weight is associated with cancer in general is by no means clear. On the other hand, it has been demonstrated that overweight women more often feel like they get a negative reception from their health care provider and hence do not attend cervical cancer screening opportunities as assiduously as age-matched, more slender women.

In addition to well-recognized cardiovascular consequences of obesity, risk for some cancers is also meaningfully increased. ■

DPP-4 Inhibitors: Should We Worry About Risk of Pancreatitis?

Source: Raz I, et al. *Diabetes Care* 2014; 37:2435-2441.

Although not well recognized until the advent of DDP-4 inhibitors (e.g., alogliptin, linagliptin, saxagliptin, sitagliptin) and GLP-1 agonists (e.g., albiglutide, dulaglutide, exenatide, liraglutide), diabetes is associated with pancreatitis. The mechanisms by which diabetes might lead to pancreatitis are not well understood, although comorbid hypertriglyceridemia and hypertension (which is often treated with thiazides, leading to triglyceride elevation) might be contributing factors.

In the last 2-3 years, case reports of pancreatitis in patients taking GLP-1 agonists and DPP-4 inhibitors have prompted closer scrutiny of the potential relationship between these two classes of agents. Indeed, FDA labeling for some agents from both classes includes warning/caution comments on pancreatitis. Do DPP-4 inhibitors or GLP-1 agonists increase risk for pancreatitis? Recent trial data on saxagliptin provides reassuring commentary that likely merits consideration in reference to other members of the DPP-4 group as well.

Raz et al report data from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial. Among the 16,492 patients randomized to DPP-4 treatment (saxagliptin) or placebo, the risk for pancreatitis was both small (< 0.5%) and not different between saxagliptin and placebo.

Current recommendations suggest that incident pancreatitis in patients taking DPP-4 inhibitors or GLP-1 agonists merits at least temporary discontinuation of such treatment. The SAVOR-TIMI 53 data provide reassurance that DPP-4 inhibitors, specifically saxagliptin, do not increase risk for pancreatitis. ■

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