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EDITORIAL

Brave New World: Improving Obesity and Preventing Cardiovascular Disease

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For several decades, obesity and type 2 diabetes (T2D) have been rising in tandem so that today, they are worsening global pandemics with debilitating, expensive, and often lethal complications. The prevalence of T2D in the United States has risen more than 10-fold from 2.5 million in 1959 to more than 25 million in 2022.[1] During the same time frame, obesity has risen 4-fold, so that now it affects 40% of US adults and is the leading cause of preventable disease and premature mortality. About 90% of people with T2D are overweight or obese, and traditional drugs for T2D, including insulin, sulfonylureas, and thiazolidinediones, cause further weight gain.[1] Even when hemoglobin A_{1c} levels are well controlled using these older glucose-lowering therapies, approximately two-thirds of patients with T2D die of cardiovascular disease (CVD) causes.[2,3]

Insulin Is Cardiotoxic

In 1921, Dr Frederick Banting discovered the first effective glucose-lowering agent by extracting insulin from the pancreases of fetal calves and using it in his diabetic patients.[1] A century later, we have 13 classes of glucose-lowering drugs, comprising hundreds of US Food and Drug Administration (FDA)—approved medications for the management of T2D. Although all of these drugs lower serum glucose levels, not a single one had been proven to reduce the alarmingly high risk of CVD death among people with diabetes until 2015, when the EMPA-REG Outcome study using empagliflozin was published.[1]

Insulin is one of the key drivers of CVD in T2D. Chronically elevated blood insulin levels predispose to inflammation, hypertension, atherogenic dyslipidemia, atherosclerosis, fluid retention, heart failure (HF), and arrhythmias.[4] Injected insulin in patients with T2D predictably causes weight gain and can trigger hypoglycemic spells. Prospective observational studies have consistently reported that exogenous insulin for patients with T2D is associated with increased risk of myocardial infarction, ischemic stroke, and CVD mortality in a dose-dependent relationship.[4] Furthermore, multiple randomized controlled outcome trials implicate injected insulin as a potential contributor to increased risk of CVD, HF, and all-cause mortality among patients with T2D (Figure 1).[4,5]

Likewise, sulfonylureas reduce serum glucose levels by stimulating pancreatic beta cells to secrete more insulin; so, as with injected insulin, these agents stimulate weight gain and predispose to hypoglycemia. Randomized trials of sulfonylureas have reported increased risks for CVD, as evidenced by the fact that all sulfonylureas carry an FDA "black box" warning regarding an increased risk for CVD mortality.[1] Thus, for many patients, the use of insulin and sulfonylureas should be carefully considered, given the availability of other agents.

Lifestyle Improves CVD Risk in Diabetes

Lifestyle strategies can produce weight loss and improve prognosis in the setting of T2D. Zhang and colleagues[3] reported in this issue of *Mayo Clinic Proceedings* that individuals with T2D who followed a healthy lifestyle had significantly lower risks of incident CVD and all-cause mortality. This was a large meta-analysis of 5 international prospective studies comprising more than 100,000 individuals with T2D (about 50% were from the United States, with about 25% each from China and the United Kingdom); 92.5% of the participants were diagnosed with diabetes when they were older than 30 years.

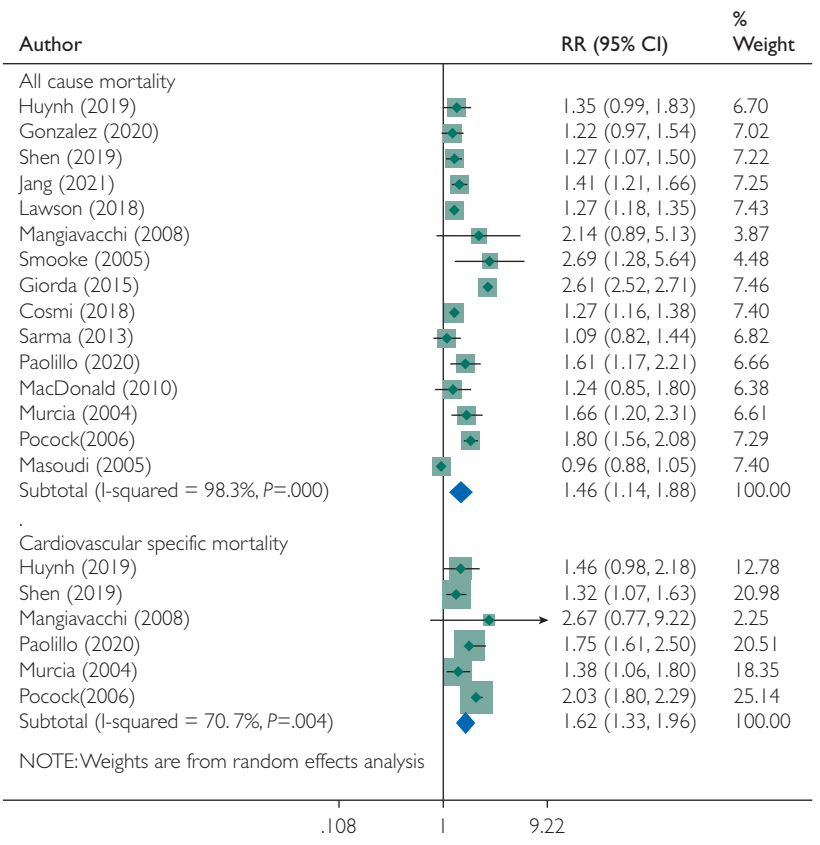

FIGURE 1. Injected insulin among diabetic patients with heart failure was associated with increased risk of mortality, hospitalization, and readmission compared with noninsulin therapies.[5] RR, relative risk.

The 5 healthy lifestyle factors assessed were having an optimal bodyweight, following a healthy diet, performing regular physical activity, being a nonsmoker, and drinking a low to moderate amount of alcohol regularly.[3] Study participants following 4 or 5 healthy lifestyle factors compared with those following only 1 or none had a highly statistically significant 40% reduction in risk of all-cause mortality during a median follow-up of 10 years. Attaining each single healthy lifestyle factor was associated with a statistically significant 16% lower risk of death during the study. Individuals following 4 or 5 healthy lifestyle factors compared with those following only 1 or none also experienced a highly statistically significant 33% reduction in CVD risk (defined as fatal and nonfatal ischemic heart disease and stroke).

Without question, a healthy lifestyle is strongly correlated with a favorable CVD prognosis and improved life expectancy in patients with T2D, as is the case in people without diabetes. However, lifestyle-based weight loss strategies, such as diet and exercise, although often effective in the short term, are less effective in the long term because most obese individuals tend to regain the excess adipose tissue. Therefore, safe and effective drug therapy to facilitate and to maintain weight loss for individuals with obesity or T2D is an important unmet need.

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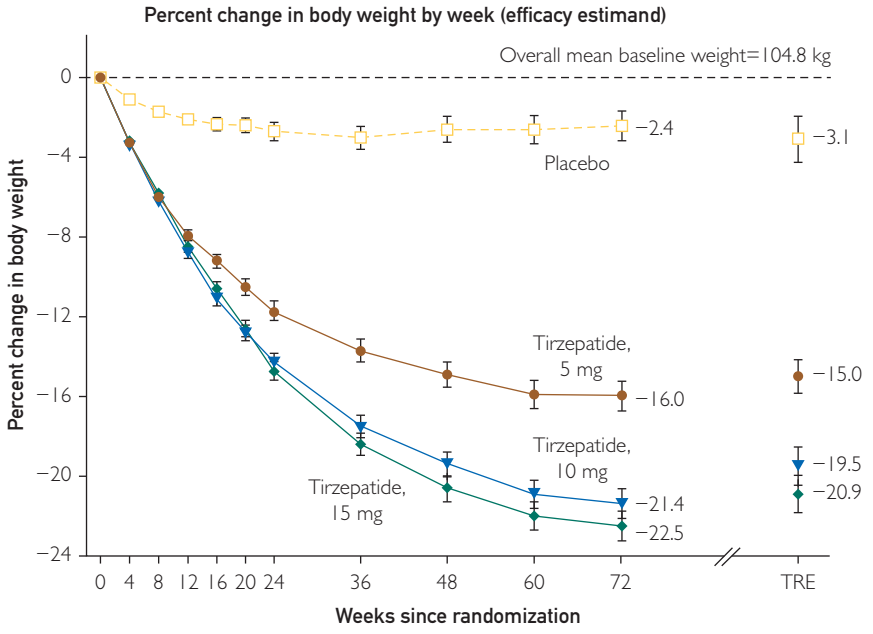

FIGURE 2. Tirzepatide at escalating doses significantly reduced weight vs placebo.[9]

Safe and Effective Drugs for T2D and Weight Loss

In the past 7 years, many randomized outcome trials of sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have proven that these 2 classes of diabetic drugs confer remarkable reductions in risk of CVD as well as unprecedented and safe weight loss in the setting of obesity.[1,6] Large randomized controlled trials find that these agents confer protection against major CVD events (especially among patients with established atherosclerotic CVD), improve symptoms and prognosis for HF regardless of left ventricular ejection fraction, reduce risk of progression of chronic kidney disease, reduce blood pressure, and decrease risk of both CVD mortality and all-cause mortality.[1,2,7] Notably, SGLT2 inhibitors and GLP-1 RAs are effective for improving prognosis for many of these conditions even in patients without T2D.[6]

Weight loss, in the setting of obesity and T2D, will improve many CVD risk factors, including hyperglycemia, dyslipidemia, hypertension, hepatic steatosis, and obstructive sleep apnea; substantial weight loss can even sometimes induce T2D "remission." Semaglutide and liraglutide are GLP-1 RAs that are FDA approved for weight loss. These agents lower body weight up to about 5% to 15% by slowing gastrointestinal motility and increasing satiety.[6,8] The weight loss is gradual as the dose is titrated up during 3 to 6 months. SGLT2 inhibitors are oral agents that are not approved for weight loss but stimulate modest decreases in body weight, typically 3% to 4% in obese individuals.[8] Even so, the weight loss is additive when an SGLT2 inhibitor is used with a GLP-1 RA, and the quantity of adipose tissue lost can be substantially enhanced if insulin therapy, sulfonylureas, or thiazolidinediones can be tapered or discontinued.[1,8]

Tirzepatide, a novel once-weekly injection that represents a new class of pharmacologic agents being studied for the treatment of obesity and T2D, is a single peptide that activates the body's receptors for 2 natural incretin hormones, GLP-1 and glucose-dependent insulinotropic

polypeptide. Although it is approved for treating T2D, tirzepatide is demonstrably the most effective drug for weight loss ever developed. In a randomized placebo-controlled clinical trial of obese persons, low-dose tirzepatide (5 mg/wk, injected subcutaneously) produced a 15% reduction of body weight; full-dose therapy (15 mg/wk) lowered weight by 21% (about 50 pounds; Figure 2).[9] Tirzepatide also reduced waist circumference, serum lipid concentrations, fasting insulin concentration, hemoglobin A_{1c} levels, and systolic and diastolic blood pressure. Adverse events were limited to gastrointestinal symptoms, such as nausea, diarrhea, and constipation, similar to those associated with GLP-1 RAs.

Summary

Lifestyle strategies are effective for improving cardiovascular health and longevity in people with T2D and should be first-line therapy. For the first time, we also have safe and effective drugs for improving CVD prognosis and reducing weight in patients with obesity and T2D, although these agents are highly underused.[10] In the future, lifestyle modification in conjunction with appropriate use of these new glucose-lowering therapies will likely be the preferred therapeutic approach to obesity and T2D.

POTENTIAL COMPETING INTERESTS

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