MANAGEMENT OF OVERWEIGHT/OBESE PATIENTS WITH T2DM

In this Issue...

The "diabesity" epidemic – the rising number of obese and overweight patients attempting to control their type 2 diabetes – continues to present a conundrum to treating clinicians. Weight loss will improve glycemic control, but patient adherence to effective diets is very often difficulty to maintain. A further complication is that often-prescribed pharmacotherapies are known to induce weight gain.

In this issue, we review the recent evidence describing how GLP–1 agonists may be appropriate at many different stages of T2DM.

In this issue, we review the current literature describing:

- The cardiovascular effects of intensive lifestyle intervention
- The comparative success of weight loss among named diet programs
- Current pharmacotherapies available to treat overweight or obese patients with type 2 diabetes
- The MGI (metformin, GLP-1, insulin) approach to glycemic and weight control
- The latest evidence regarding bariatric surgery as treatment for diabetes in overweight or obese patients.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the impact of healthy lifestyle in improving diabetes in overweight or obese adults.
- Describe pharmacological approaches to obesity treatment in adults with type 2 diabetes for intensifying diabetes medications without inducing weight gain.
- Evaluate surgical approaches to obesity treatment in adults with type 2 diabetes.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.
position to control the content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships regardless of their relevance to the content of the activity. Faculty are required to disclose only those relationships that are relevant to their specific presentation. The following relationship has been reported for this activity:

**IMPORTANT CME/CE INFORMATION**

**GUEST AUTHOR OF THE MONTH**

**Commentary:**
Clare J. Lee, MD  
Instructor of Medicine  
Johns Hopkins University School of Medicine  
Baltimore, Maryland

**Guest Faculty Disclosure**
Clare J. Lee, MD has indicated that she has no financial relationships with commercial supporters.

**Unlabeled/Unapproved Uses**
Clare J. Lee, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

**Program Directors’ Disclosures**

**IN THIS ISSUE**

**COMMENTARY from our Guest Author**

**CV EFFECTS OF INTENSIVE LIFESTYLE INTERVENTION IN T2DM**

**COMPARISON OF WEIGHT LOSS AMONG NAMED DIET PROGRAMS**

**UPDATE ON OBESITY PHARMACOTHERAPY**

**PHYSIOLOGICAL AND WEIGHT-FOCUSED TREATMENT STRATEGIES FOR MANAGING T2DM WITH METFORMIN, GLP-1 RA, AND INSULIN (THE MGI APPROACH)**

**GASTRIC BYPASS AND SLEEVE GASTRECTOMY FOR TYPE 2 DIABETES**

**Program Directors**

Nestoras Mathioudakis, MD  
Assistant Professor of Medicine  
Division of Endocrinology, Diabetes and Metabolism  
Associate Director, Inpatient Diabetes Management  
Johns Hopkins University School of Medicine  
Baltimore, Maryland

Om P. Ganda, MD  
Associate Clinical Professor of Medicine  
Harvard Medical School  
Senior Physician and Director, Lipid Clinic  
Chair, Clinical Oversight Committee  
Joslin Diabetes Center  
Boston, Massachusetts

Susan Porter, MSN, CRNP, CDE  
Clinical Nurse Practitioner and Certified Diabetes Educator  
Johns Hopkins University School of Medicine  
Baltimore, Maryland
With rising diabetes and obesity rates around the world, clinicians often face the challenge of treating patients with both diseases. Against this “diabesity” epidemic, we have made important strides within the past several decades to better understand the roles of lifestyle modification, pharmacotherapy and surgery. Healthy lifestyle focused on low-carbohydrate and/or low-fat diet plus regular exercise is vital in promoting overall health as well as in improving both diabetes and obesity.

In a large longitudinal study of over 5000 adults followed over 10 years, the Look AHEAD research group demonstrated that obese adults with type 2 diabetes (T2DM) can lose weight and maintain modest weight loss through intense lifestyle intervention. Regarding the optimal diet for overweight and obese individuals, a recent meta-analysis by Johnston et al in JAMA showed no evidence to support one type of major named diet over another. Rather, it appears that any diet that a patient will adhere to with the intention of losing weight will be the best diet for weight loss.

The number of medications recently approved to treat diabetes and/or obesity alone speaks to the speed at which our medical community is tackling these problems; between 2006 to the present, a total of 16 diabetes medications and 4 obesity medications (either new or combinations of previously approved medications) were approved by the Food and Drug Administration. Given this exciting pace of development in pharmacotherapy to treat T2DM and obesity, clinicians now have a selection of choices for initiating a pharmacotherapy in a patient with T2DM whose glycemic control remains off-target despite healthy lifestyle. The (reviewed herein) Bray and Ryan article provides a detailed review of available pharmacotherapies to treat obesity and separately discusses pharmacotherapies available to treat obesity in those with T2DM. Nadeau provides an endocrinologist’s perspective in prioritizing the pharmacotherapies for T2DM that are weight-neutral or weight-loss promoting. Specifically, metformin, glucagon-like peptide (GLP)-1 receptor agonists, and DPP4 inhibitor are pharmacotherapies that do not promote weight gain and should be considered strongly in overweight or obese patients with T2DM. Yet another new pharmacotherapy to consider, albeit with limited longitudinal data, are the sodium-glucose cotransporter (SGLT)-2 inhibitors, which lower hemoglobin A1c with modest weight loss benefit. While the increasing number of pharmacotherapy choices available for T2DM may provide new challenges for clinicians, metformin should be considered first-line whenever possible, followed by a GLP-1 agonist or DPP4 inhibitor in T2DM patients who are overweight or obese.

When healthy lifestyle and pharmacotherapy are insufficient to treat overweight or obese patients with T2DM, weight-loss surgery such as Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) should be considered. Over the past several decades, we have increasing data suggesting the role of weight-loss surgery as the most effective treatment for obesity and T2DM. Currently, the NIH criteria to undergo weight-loss surgery include body mass index (BMI) ≥ 40 kg/m2 or ≥ 35 kg/m2 with comorbidities such as T2DM, sleep apnea, or hypertension. In a systemic review of 33 human studies, Yip et al reported similar T2DM remission rates between RYGB and SG at up to three years after surgery (defining diabetes remission as hemoglobin A1c > 6% without the use of diabetes medications). T2DM remission was observed in over 80% of the patients at 36 months for both surgical interventions.

It is important to note that while these results are quite impressive, only three of the 33 studies included in this review were randomized trials. A more recent study by Schauer et al reported the results of the randomized trial of bariatric surgery versus intensive medical therapy at year 3. The authors of this study confirmed a significantly greater number of individuals with hemoglobin A1C of 6% or less in the surgical group (38% in RYGB and 24% in SG) compared to the intensive medical therapy group (5% at year 3. Similarly, patients in the surgical group lost more weight (24.5% in RYGB, 21.1% in SG) compared to those in the intensive medical therapy group (4.2%) at year 3. More rigorous studies focused on longitudinal outcomes of bariatric surgery are needed to elucidate the long-term benefits and risks related to bariatric surgery.
The cornerstone of treatment of both T2DM and obesity is healthy lifestyle, through which low-carbohydrate, low-fat diet, daily regular exercise should be emphasized. When these efforts fail, metformin should be considered first-line therapy, given its efficacy in lowering the hemoglobin A1c, modest weight-loss benefit, and low cost. Next, GLP-1 agonists or DPP4 inhibitors should be considered, given their efficacy in improving glycemic control and weight-neutral or modest weight-loss benefits. In those who qualify, bariatric surgery is an effective treatment that should be considered, especially in those with extreme obesity and subsequent comorbidities such as lack of mobility, sleep apnea, and hypertension. The mechanisms behind effective and durable improvement in diabetes after bariatric surgery may be partly mediated by changes in gut hormones. In turn, understanding the mechanisms of how bariatric surgical intervention achieves metabolic improvement may provide future targets of medical therapy for treatment of diabetes and obesity.

References
The primary end point was the first occurrence of predefined cardiovascular outcome such as death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, as well as hospitalization for angina. The secondary end points also included death from any cause, myocardial infarction, stroke, coronary artery bypass grafting, percutaneous coronary intervention, and hospitalization for heart failure or peripheral vascular disease. Although the authors anticipated a maximal follow-up period of 11.5 years, the study was stopped early at median follow up of 9.6 years on the basis of futility analysis.

In the study, the intervention group achieved more weight loss and greater fitness compared to the control group with mean weight loss of 7.9% at one year and 2.5% at the end of the study over the control group. Surprisingly, however, there were no significant differences in cardiovascular outcomes between the two groups.

In summary, this study showed that an intensive lifestyle intervention did not reduce the risk of cardiovascular disease, as compared with a control regimen of diabetes support and education among overweight or obese patients with type 2 diabetes. The lack of significant between-group difference may be because weight loss in the intervention group was inadequate to reduce the cardiovascular risk, or the rigorous medical management of cardiovascular risk in the control group making the between-group difference too small to detect.

While the authors failed to show that the reduction of cardiovascular risk in the intervention group was greater than in that of the control group, they succeeded in demonstrating various other important benefits of sustained weight loss through intensive lifestyle intervention, such as improvement in glycemic control, quality of life, physical function, and mobility, as well as reduction in urinary incontinence, sleep apnea, and depression. Therefore, weight loss through healthy lifestyle remains a cornerstone of treatment of type 2 diabetes in overweight or obese adults.

References

COMPARISON OF WEIGHT LOSS AMONG NAMED DIET PROGRAMS


In this 2014 publication, the authors sought to determine weight loss outcomes for major named diets. While named weight loss programs in the United States represent a multibillion-dollar industry (with each program claiming superiority over the others), there is a paucity of rigorous studies comparing these programs for the benefit of the consumers. Therefore, the authors of this article aimed to evaluate the effect of each named diet through network meta-analysis of available randomized clinical trial (RCT) data.

In the study design, authors included in the meta-analysis RCTs that assigned overweight or obese adults to a popular branded diet or an alternative with at least three months' follow up thereafter. The primary outcomes were weight loss at six- and 12-month follow-up, and secondary outcomes were BMI and adverse events. The authors searched six electronic databases using keywords such as RCTs, diets, adults, and weight loss. Pairs of reviewers independently screened articles and independently extracted data and assessed selected studies for risk of bias associated with each trial.
The authors selected 48 RCTs in this meta-analysis, which included a total of 7286 individuals with median age of 45.7 years and median BMI of 33.7. A total of 12 trials among the 48 RCTs included patients with type 2 diabetes. Overall, the authors found that a low-carbohydrate and low-fat diet led to more weight loss (up to 4 kg) than no dietary intervention at one year. They also found no significant difference in weight loss between individual diets. Combined with the fact that people tolerate different diets variably, there is no evidence to support one diet over the other. The strengths of this review include the use of network meta-analyses, a comprehensive literature search, assessment of risk of bias, and systematic review of the potential harms of named diets. The study's weaknesses include substantial heterogeneity between studies, limited data on calorie restriction, and high risk of bias in 19 RCTs related to missing participant outcome data.

The important lesson in this study is that any diet that a patient will adhere to with the intention of losing weight appears to be the best diet. In agreement with prior studies by American Heart Association and the Obesity Society, this review did not find adequate evidence to recommend a particular diet.\(^1\,^2\)

References
Regarding drugs approved for short-term use in treating the patients with obesity, the authors discuss the sympathomimetic drugs such as benzphetamine, diethylpropion, phendimetrazine, and phentermine. The phentermine group achieved a mean weight loss of 2.5% over treatment with placebo at six months. Common side effects include dry mouth, insomnia, and increased heart rate and blood pressure.

For treating obesity in patients with type 2 diabetes, the authors discuss metformin, glucagon-like peptide-1, pramlintide, and sodium-glucose cotransporter (SGLT)-2 inhibitors.

- Metformin is the cornerstone of type 2 diabetes treatment, and its effect on weight loss was established in the Diabetes Prevention Program study (DPP). In this study, the metformin group lost on average 4 kg over the placebo group at two years.
- Liraglutide, a glucagon-like peptide (GLP)-1 agonist, was voted favorably by an FDA panel for treatment of obesity in September 2014 (after publication of this study).
- Pramlintide is a modified form of amylin that produced weight loss similar to that of the GLP-1 agonists. However, it has not been in wide use because it requires frequent dosing.
- The SGLT2 inhibitors approved by the FDA for diabetes treatment (at this time) are dapagliflozin, canagliflozin, and empagliflozin. These SGLT2 inhibitors led to weight loss of up to 2.3 kg compared to placebo. Side effects included urinary tract infections and hypoglycemia.

Of note, it is important to remember that all weight-loss medications are contraindicated in pregnancy. Topiramate use requires a negative pregnancy test before use because of its association with oral clefts.

References
sulfonylureas and insulin. Fortunately, several diabetes medications are weight-neutral or weight-loss promoting, and they should be strongly considered when clinicians want to intensify treatment of T2DM in patients with obesity.

The cornerstone of T2DM treatment and prevention consists of healthy lifestyle. Healthy diet and exercise have tangible impacts on type 2 diabetes and can delay the initiation of diabetes medications or allow dose reduction or elimination of current pharmacotherapies. Regarding healthy diet, plant-based diets rich in whole grains, fruits, vegetables, and nuts have shown benefits in weight loss and improved insulin sensitivity. In one study, a low-fat, vegan diet lowered the hemoglobin A1c by 0.4% and weight by 1.4 kg at 74 weeks over a diet following the 2003 American Diabetes Association guidelines. While a vegan diet may not be realistic for many patients, the study is useful in highlighting the impact of healthy diet in glycemic control and weight loss.

When starting medications in patients whose glycemic control remains off-target despite adherence to a healthy lifestyle, the author recommends metformin first, followed by a glucagon-like peptide (GLP)-1 agonist and insulin. Metformin is the first-line treatment for T2DM, as recommended by many professional organizations because of its effectiveness in lowering the hemoglobin A1c, low cost, and its weight-neutral or modest weight-loss promoting properties. If a patient with T2DM needs further therapy intensification, the author recommends GLP-1 agonist as the next line of treatment, given its dual roles in glycemic control and weight loss. For those who require further intensification of therapy, the author recommends the addition of basal insulin, which is an effective therapy, albeit promoting weight-gain, to rapidly lower the hemoglobin A1c. Alternatively, clinicians may consider adding a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a newly approved class of medications for T2DM that work by inhibiting glucose reabsorption in the renal proximal tubule. This medication has the added benefit of a modest weight-loss promoting property, which should be taken into consideration, especially for patients who would like to delay using insulin. However, as these are newer agents, their long-term effects on cardiovascular or microvascular outcomes and their safety profile are not well-defined.

In conclusion, clinicians should consider diabetes medications that are weight-neutral or weight-loss promoting when initiating pharmacotherapy in overweight or obese patients with T2DM. Specifically, clinicians should consider metformin, GLP-1 receptor agonists, and most recently, SGLT2 inhibitors as treatment options to help avoid further weight gain in these patients.

References
SG is a newer procedure involving the creation of a gastric sleeve tube without rerouting of the small intestine. T2DM remission was defined in this paper as being off diabetes medications with normal fasting glucose or a hemoglobin A1c of < 6%. Weight loss was assessed by percent excess weight loss and percent excess BMI loss.

The goal of this paper was to determine whether GBP is superior to SG in achieving T2DM remission and weight loss. The authors performed a systematic review and meta-analysis of the current evidence in the literature, searching the PubMed and Embase databases to find clinical studies that reported both of the relevant outcomes. The authors analyzed in detail a total of 33 studies, which included three randomized controlled trials and 30 nonrandomized studies. Only five studies had both GBP and SG as treatment arms, while the rest of the other studies reported outcome either on GBP or SG. The follow up in these studies ranged from three to 36 months following surgery.

The main findings of this meta-analysis were that there were no significant differences in diabetes remission rates or weight loss between GBP and SG at one year. Both procedures caused substantial and rapid improvement in T2DM, which led to T2DM remission rate of 67% for GBP and 56% for SG at three months and 76% and 68%, respectively, at 12 months. For weight loss outcome, the authors found a mean excess weight loss of 65% after GBP and 66.8% after SG at 12 months. The strengths of this study include strict definition of diabetes remission after bariatric surgery, which is in agreement with the latest recommendation of the American Diabetes Association (ADA), as well as rigorous methods to minimize the selection bias and attrition bias. The weaknesses of this study include the paucity of randomized controlled studies comparing GBP and SG and the lack of consensus on the definition of T2DM remission across the literature, which led to a reduction in the number of eligible studies.

This review confirms the potent effect of GBP and SG in T2DM remission and weight loss. Although the longitudinal data on the outcome of SG are lacking (because it is a newer bariatric procedure), it appears that SG has metabolic benefits comparable to that of GBP at one year. Therefore, both GBP and SG are reasonable surgical treatment options in obese individuals with T2DM. More studies directly comparing these two procedures focused on long-term outcome are needed to better tailor bariatric surgery procedures to meet individual patient needs.

References
CREDIT DESIGNATION STATEMENT
Physicians
eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
eNewsletter: This 1 contact hour educational activity is provided by the Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1 contact hour or a total of 6 contact hours for the six newsletters in this program.

Podcast: This 0.5 contact hour educational activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hours or a total of 3 contact hours for the six podcasts in this program.

SUCCESSFUL COMPLETION
To successfully complete this activity, participants must read the content, and then link to the Johns Hopkins University School of Medicine's website or the Institute for Johns Hopkins Nursing's website to complete the post-test and evaluation. A passing grade of 70% or higher on the post-test/evaluation is required to receive CE credit.

LAUNCH DATE
November 25, 2014; activities expire 2 years from the date of publication.

There are no fees or prerequisites for this activity.

INTERNET CME POLICY
The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM CME maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in an Internet-based CME program. Your information will never be given to anyone outside of the Johns Hopkins University School of Medicine's CME program. CME collects only the information necessary to provide you with the services that you request.

DISCLAIMER STATEMENT
The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

STATEMENT OF RESPONSIBILITY
The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

POLICY ON FACULTY AND PROVIDER DISCLOSURE
As a provider approved by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Johns Hopkins University School of Medicine Office of Continuing Medical Education (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control the content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships regardless of their relevance to the content of the activity. Faculty are required to disclose only those relationships that are relevant to their specific presentation. The following relationships have been reported for this activity:

Guest Author Disclosures

CONFIDENTIALITY DISCLAIMER FOR CONFERENCE ATTENDEES
I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and the federal HIPAA privacy regulations (the Privacy Regulations). Protected health information is information about a person's health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential. I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

"The Office of Continuing Medical Education at The Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only."

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine Office of Continuing Medical Education Turner 20/720 Rutland Avenue Baltimore, Maryland 21205-2195

Reviewed and Approved by General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS
Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.
COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST