AADE American Association of Diabetes Educators

AADE PRACTICE PAPER

Addressing Obesity In Diabetes

Reviewed by the AADE Professional Practice Committee
August 2018

Obesity continues to be an epidemic with approximately 36.5% of all adults in the United States deemed obese.1 As recently as 2013-2014, the prevalence of obesity was reported to be 40% in women and 35% in men.2 If current trends continue, it is projected that by the year 2030, 51% of the population will be obese.3 Considering the prevalence of obesity and its associated comorbidities (i.e. diabetes, cardiovascular disease, hypertension, osteoarthritis, etc.), the economic burden is substantial.4-8 The estimated cost of obesity ranges from $147 billion to nearly $210 billion per year.9 Individuals who are obese have been found to spend $628 to $756 more on healthcare annually compared to normal-weight individuals.10 Additionally, obese persons with diabetes or metabolic syndrome have been shown to have a lower health-related quality of life.11 More specifically, obesity is a major contributor to the type 2 diabetes (T2DM) epidemic where nearly 88% of those with T2DM are considered overweight or obese.6-8 Despite the increased risk of poor clinical outcomes and negative impact on quality of life, only one-half of individuals with diabetes and other chronic conditions receive counseling on diet and/or exercise by their primary care provider.12-13

Diabetes and Obesity Connection

Obesity is a multifactorial disease that is typically said to occur when energy intake exceeds energy expenditure over a long period. Genetic, environmental, and lifestyle factors impact energy and body weight status such as: hormones signaling hunger, availability of palatable foods, habit forming preferences, and gut microbiome.

Epidemiological research has documented the association between the nutritional status early in life and lifestyle habits with the development of obesity and chronic diseases. Eating behavior is regulated by two competing mechanisms the homeostatic and hedonic drive to eat. The homeostatic mechanism is the biologic control as compared to the hedonic is the reward means for managing appetite. Research points to an "obesogenic environment," meaning that there are external factors contributing to hormonal imbalances, overeating and alterations in the hedonic response to food. For example, sleep deprivation leads to an alteration in appetite regulating hormones, particularly ghrelin thus increasing hunger and heightened hedonic response.[14] Just expanding a person's sleep to six hours improved body composition by decreasing fat mass gain.

Weight gain is decreased by leptin and other hormones that induce satiety, including gut-derived hormones. Leptin is generated from the adipocytes and is key to regulating body fat mass and weight. With weight loss, leptin levels decrease. This decrease results in compensatory mechanisms that both reduce energy expenditure and encourage weight (re)gain.[15, 16]

Leptin and ghrelin are other endocrine hormones involved in energy and appetite signaling. Leptin is secreted by adipocytes in proportion to their triglyceride content and is associated with maintaining long-term energy status. The typical signaling of leptin works to decrease food intake and increase energy expenditure.[15-17] During energy restriction and weight loss, leptin levels are decreased and are associated with numerous metabolic abnormalities related to visceral obesity (hunger, decreased metabolic rate, insulin resistance, etc.). Paradoxally, obesity is often correlated with increased leptin levels giving rise to the hypothesis of "leptin resistance." [15-17] Ghrelin is a gut hormone associated with short term energy maintenance through signaling in meal initiation and termination. The typical signaling of ghrelin works to stimulate appetite, followed by a corresponding fall in circulating ghrelin levels in response to dietary

consumption. This postprandial reduction of ghrelin has been shown to be blunted, or even absent in obese persons.[17]

The relationship between hyperinsulinemia, insulin resistance, and obesity has remained unresolved for decades. Insulin is responsible for postprandial use and storage of nutrients, which includes inhibiting fatty acid oxidation and increasing lipogenesis. Fasting and postprandial hyperinsulinemia occur as a response to systemic insulin resistance in an attempt to maintain glucose homeostasis.[18] Hyperinsulinemia directly contributes to the development of excess lipid accumulation [obesity] in several tissues. Genetic research has shown this as a cyclic positive feedback loop where hyperinsulinemia promotes obesity, which in turn increases insulin resistance and furthermore encourages obesity.[18]

Gut microbiome plays a pivotal role on macronutrient metabolism, insulin resistance, and inflammation. Bacteria in the gut is required for maintaining energy homeostasis, insulin signaling, and immunity, and modulating inflammation. Alterations in gut microbiota can lead to dysbiosis contributing to metabolic disorders such as T2DM separately and in concurrence with obesity.[19] Research demonstrates that dietary and environmental factors affect gut microbiota, with low diversity being associated with changes in metabolic markers including increased serum leptin, insulin resistance, and increased high sensitive C-reactive protein (hsCRp) and decreased adiponection.[20-22] The importance of these changes lead to gut-derived metabolites and microbes such as lipopolysaccharides and short chain fatty acids influencing metabolic pathways such as insulin signaling, appetite regulation, incretin production, and inflammation. Gut dysbiosis can be attenuated through dietary modifications. Dietary or supplemental intakes of pre- and probiotics cause positive changes in gut integrity, increased satiety, improved insulin sensitivity, and improved energy homeostasis and the loss of excess body weight. In addition to the effects of dietary and environmental factors, medications can influence gut flora and in turn inhibit weight loss through mechanisms of increased inflammation and decreased insulin sensitivity.[23-24]

Classification

Per the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), all adults should be screened annually for overweight and obesity.[25] The recommended approach is to use body mass index (BMI), which is calculated as weight in kilograms divided by height in meters squared. Normal BMI is 18.5-24.9 kg/m^2. A cutoff of ≥23 kg/m^2 defines those individuals that should be screened and further evaluated for diagnosis in South Asian, Southeast Asian, and East Asian adults, and a cutoff of ≥25 kg/m^2 for everyone else. Adults with BMI between 25 and 29.9kg/m^2 are classified as overweight and those greater than or equal to 30 kg/m2 are considered obese. Obesity is further defined by class I (30-34.9 kg/m2), class II (35-39.9 kg/m^2), and class III (≥40 kg/m2). To assess disease risk associated with obesity, the AACE/ACE guidelines recommend measuring waist circumference when BMI is <35 kg/m^2. For men, the waist circumference cutoff point for increased risk is ≥94 cm (37 inches) and in women, ≥80 cm (31.5 inches). For the Asian population, the waist circumference cutoff for men is ≥85 cm (x inches) and for women is ≥ 74 to 80 cm (29 inches to 31 inches).

Obesity and Diabetes Progression

The prevalence of prediabetes in 2015 was 33.9% of US adults.[26] The prevalence of metabolic syndrome in 2012 was 34.2%.[27] Metabolic syndrome is a cluster of interrelated metabolic risk factors including abdominal obesity and arguably has been labeled a pre-diabetic state.[28] Individuals with metabolic syndrome have a 5-fold increase in diabetes risk. Undeniably, the prevention or delay of diabetes can be achieved through the adoption and maintenance of healthy lifestyle behaviors, like those described in the National Diabetes Prevention Program (DPP).[29] Several long-term follow-ups of key trials demonstrated intensive lifestyle interventions targeting a 5-10% reduction in total body weight coupled with 150+ minutes of physical activity per week could reduce the incidence of T2DM by anywhere from 34-58%.[30-32] Incorporating 150 minutes per week of moderate intensity physical activity has shown to have many positive effects in prediabetes including improved insulin sensitivity and reduced abdominal fat.[33-35]

Additionally, obesity is a major risk factor for cardiovascular disease.[36] Obese individuals are at greater risk of cardiovascular disease (CVD) compared with normal weight individuals.[37] Maintaining weight loss of just 5%-10% of body weight can result in decreased triglycerides, systolic blood pressure, low density lipoprotein, and an increase in high density lipoprotein; all which reduce

the risk of CVD.[37-38] Reduced weight and sustained weight loss can improve glycemic control and decrease the amount of medications an individual needs.[39] Findings from the Action for Health in Diabetes (Look AHEAD) trial demonstrated that weight loss and physical activity corresponded to a marked decline in A1C and improvements in CVD risk factors.[40-41] Weight loss at any age after 20 has been shown to have life-time cost savings ranging from $16,882 to $36,278 due to a number of factors including reductions in medications, hospitalizations, outpatient visits, and emergency room visits.[42]

Management of Obesity in the Person with Diabetes

Effective education and counseling by diabetes educators as part of the comprehensive healthcare team can yield important clinical benefits while improving cost savings to both the individual and the healthcare system.[43] The American Medical Association recently recognized obesity as a disease that requires a range of medical interventions for treatment and prevention. AACE and ACE further support this classification emphasizing the role multifactorial approaches have along with diet and exercise for the treatment of overweight and obese populations.[25] Diabetes educators are in a unique position to provide continued support for lifestyle changes in obese persons with diabetes.[25]

Diabetes Self-Management Education and Support (DSMES)

It is important for the diabetes educator to address obesity as a comorbidity of diabetes through self-management and behavior change. Tools such as the AADE7 Self-Care Behaviors™ can be beneficial in helping persons diagnosed with diabetes to manage weight.[44] For example, promoting *healthy eating* and *being active* are two self-care behaviors that can help achieve weight loss, and should be used as a first-line treatment strategy for obese patients during DSMES.[45] *Healthy Coping* should also be included as managing stress and other psychosocial aspects can impact a patient's success with weight loss. The person with diabetes and educator should collaboratively develop strategies (*problem-solve*) for achieving behavior change (*reducing risks*) through appropriate goal setting based on the person's readiness to change and current abilities. Success should not only be measured in the weight loss achieved through this process, but more importantly in gradual improvements in health and well-being.

Healthy Eating

The National Standards for Diabetes Self-Management Education and Support include a nutrition education component as part of the required curriculum.[46] Diabetes educators can assist people with diabetes in gaining knowledge about the effect of food on blood glucose, sources of carbohydrates, protein, and fat, and appropriate meal planning and resources for making healthy food choices. Diabetes educators also help people understand portion sizes, read food labels, plan and prepare meals, and recognize the best times to eat to match the action of their medications. This knowledge is central to managing diabetes and addressing barriers to healthy eating.[47] Medical Nutrition Therapy (MNT) provided by registered dietitians (RDs), in combination with DSMES may further benefit the obese patient with prediabetes or diabetes. MNT involves a comprehensive nutrition assessment and addresses individualized nutrition plans taking into account comorbidities, personal food preferences, eating habits, and cultural environment all aimed to achieve the patient's desired clinical outcomes.[48] Diabetes educators who are not RDs should consider recommending physician referrals to MNT and adding RDs to their diabetes care team.[49]

Physical Activity

Increased energy expenditure through physical activity is essential for weight management and overall health.[26] Benefits may include preserving fat-free mass during weight loss and enhanced fitness along with improvements in insulin sensitivity, cardiovascular disease risk factors, and quality of life. While all persons should strive for the accumulation of 150 minutes/week of moderate-intensity physical activity (equivalent to a brisk walk) to improve chronic conditions, educators must recognize that these amounts alone may result in minimal weight loss (~2-3kg).[50-51] Indeed, exercise for a longer time can provide clinically significant weight loss or minimize weight regain long-term (i.e. 200-300 min/week) and may be recommended.[52] However, matching physical activity to the person's abilities, interests, resources and health status are important considerations when working with people ready to change their activity behavior. For in-depth physical activity prescription or advanced exercise considerations, consulting with an exercise physiologist can help the diabetes educator safely and effectively prescribe exercise for the obese person with prediabetes or diabetes.

Healthy Coping

The diabetes educator and individual collaboratively develop strategies for maintaining sustained weight loss with long-term lifestyle alterations. For example, when weight loss occurs there is a 20-25% decline in 24-hour energy expenditure and a formerly obese individual would require at least 300 kcal less per day to maintain the same body weight as an individual who was never-obese with the same current body weight. The latter illustrates how continued partnership can allow the diabetes educator to work with the person in navigating these physiological changes and improve overall health and well-being.[53-54] On going counseling is essential, in all stages of the weight-loss program, to encourage a support system for weight loss and maintence as well as discussing expectations.[49] Those who have a strong support system are more successful in maintaining their weight loss. Research demonstrates that 33% of people that fall in the obese category achieve longterm weight loss if counseling is included as part of the program[54] and assessing psychosocial influences should be considered for tailoring and individualizing weight loss maintenance programs.[55] Often individuals experiencing obesity and diabetes struggle with not only the stress related to self-care of diabetes, known as diabetes distress syndrome, but also with obesity related concerns, such as body image, guilt, society acceptance, and bias.[56-57] Therefore, establishing a referral system that includes a mental health professional as a team member, should be considered for those struggling with the psychosocial issues of both diabetes and weight management.[56-57] It is recommended that the treatment plan be evaluated on an on-going basis for changes in eating patterns and behavior.[56] In those who have undergone metabolic surgery it is recommended to assess adaptation to the medical and psychosocial changes following surgery and the need for the inclusion of mental health services.[57]

Medications

As noted, the importance of promoting and maintaining healthy eating patterns and physical activity in obese persons with diabetes are paramount, and should always be encouraged. However, for persons assessed as "high risk" and for whom nutrition therapy and physical activity has not been successful, treatment options may also include pharmacologic interventions specific to weight loss.[53, 58]

Pharmacotherapy for obesity may be considered for the following individuals: (1) failure to achieve a minimum of 5% weight loss after 6-months of a comprehensive lifestyle intervention; (2) BMI greater than or equal to 30kg/m^2; or (3) BMI between 27 and 29.9 kg/m^2 with at least 1 indication for increased risk of CVD. Pharmacotherapy helps to reinforce lifestyle interventions and should always be in adjunct to diet, physical activity, and behavior therapy [59-61] See the Pharmacotherapy section for more detailed information on medication options.

Diabetes educators can play an important role in providing evidence-based medication management.[25,44,47,52, 58] Therefore, in addition to glycemic control, educators should work with providers when considering the effects of various therapeutic options on bodyweight and when advising treatment strategies. Drugs commonly associated with weight gain include glucocorticoids, certain antidiabetic medications (sulfonylureas, insulin, thiazolidinediones), antidepressants (amitriptyline, imipramine, nortriptyline, SSRIs), antipsychotics (clozapine, quetiapine, risperidone), and antiepileptic medications (gabapentin, carbamazepine, and valproic acid).[59-60] Weight gain is observed through slowing of the metabolic rate, appetite stimulation, fluid retention, hypoglycemia, or decrease in glycosuria.[60] Intensive glycemic control through pharmacotherapy (i.e. sulfonylureas, TZDs, insulin, etc.) has been linked to weight gain in both type 1 and type 2 diabetes.[61-62] This weight gain can promote hyperglycemia (through insulin resistance), hypertension, hyperlipidemia and additional cardiac risk factors and comorbid conditions.[63] Hence, treating diabetes in the obese patient with medications that are weight neutral (i.e. metformin, DPP-4 inhibitors, SGLT-2), induce weight loss (ie GLP-1), or minimize weight gain should be advised when appropriate.[57]

Current FDA approved therapy includes Orlistat (Xenical and Alli), Belviq (locaserin hydrochloride), Qsymia (phentermine and toprianate extended release), Contrave (naltrexone ER and bupropion ER), and Saxenda (liraglutide).[64] The pharmacological actions of these medications vary and require the person to deliberately and consciously alter their behavior for significant weight loss to occur. Diabetes educators often encounter people with diabetes who are overweight or obese and are eligible for weight loss medications. Therefore, it is important for diabetes educators to be familiar with the available weight loss medications along with their mechanism of action, dosages, adverse effects, contraindications and

special considerations. A diabetes educator who is familiar with these medications can be an advocate for the person and make suggestions for potential weight loss medications when appropriate. It is important to note that weight loss medications may be particularly beneficial for weight loss maintenance in those persons who lose weight via intensive lifestyle strategies

Table 1: Pharmacotherapy Options

	Orlistat (Xenical/Alli)	**Lorcaserin (Belviq)**	**Phentermine/ Topiramate ER (Qsymia)**	**Naltrexone ER/ Bupropion ER (Contrave)**	**Liraglutide (Saxenda)**
Mechanism of Action	Pancreatic and gastric lipase inhibitor	Selective 5-HT_{2C} agonist	Sympathomimetic; amine/GABA modulator and carbonic anhydrase inhibitor	Opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor	GLP-1 receptor agonist
Dose and Route of Administration	60 mg by mouth three times daily (OTC); 120 mg three times daily (prescription)	10 mg by mouth twice daily (Immediate release); 20 mg once daily (extended release)	3.75 mg/23 mg by mouth once daily for 14 days, titrate to 7.5 mg/46 mg for 12 weeks. If at least 3% weight not lost, discontinue or titrate to 11.25 mg/69 mg for 14 days, then titrate to 15 mg/92 mg	8 mg/90 mg by mouth in the morning for 1 week, titrated to 8 mg/90 mg twice daily for 1 week, then to 16 mg/180 mg in the AM and 8 mg/90 mg in the evening for 1 week, and then 16 mg/180 mg twice daily	0.6 mg injected subcutaneously once daily for 1 week, titrate by 0.6 mg daily at weekly intervals until 3 mg is reached
Contraindications	Chronic malabsorption syndrome, cholestasis, pregnancy	Pregnancy	Hyperthyroidism, glaucoma, within 14 days of MAOI therapy, pregnancy	Concomitant use of bupropion-containing products, chronic opioid use, opiate agonist, acute opioid withdrawal, uncontrolled hypertension, seizure disorder, bulimia, abrupt discontinuation of alcohol, use with benzodiazepines, barbiturates, antiepileptic drugs, MAOI, initiation of naltrexone/bupropion, or pregnancy	History of family history of medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2, pregnancy
Adverse Effects[a]	Oily rectal leakage, flatulence with discharge, abdominal	Headache, dry mouth, dizziness, nasopharyngitis,	Insomnia, dry mouth, constipation, paraesthesia,	Nausea, constipation, headache, vomiting, dizziness, insomnia	Nausea, vomiting, hypoglycemia, diarrhea, constipation,

	distress, steatorrhea, bowel urgency, oily evacuation, fecal incontinence, headache	hypoglycemia, upper respiratory tract infection, fatigue	increased heart rate (dose dependent) insomnia, dizziness, dysgeusia		headache, increased heart rate
Mean Weight Loss in Clinical Trials[b]	~3 kg	~0.5-5.8%	~5.1-10.9%	~8.2-11.5%	~6-8%

[a]Common adverse effects and drug interactions listed are those identified in Lexi-Comp and in clinical trials,
[b]Mean weight loss compared to placebo identified from clinical trials with 1 year duration,
Information from 1) LexiComp Online. Accessed February 22, 2018; and 2) AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocrine Practice 2016;22(3).

Surgical Considerations

Bariatric surgery can reduce the size of the stomach reservoir, limiting the amount of food that can be eaten as well as affecting absorption of nutrients.[65-69] Common types of bariatric surgery procedures include: laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG), laparoscopic Roux-en-Y gastric bypass (RYGB), and laparoscopic biliopancreatic diversion (BPD), BPD/duodenal switch (BPD-DS). Each procedure has different processes and end-results. The LAGB procedure places a band around the stomach, semi permanently alter the size.[69] The LSG procedure resects the stomach permanently removing about 80% of the stomach. The RYGB transects the stomach to form a smaller pouch reducing both volume and decreasing absorption and the BPD-DS procedure combines the previous transection with about 75% removal of the stomach.

People are considered candidates for evaluation for surgery if they meet one of three conditions: (1) BMI greater than or equal 40 kg/m^2 without coexisting medical problems; (2) BMI greater than or equal to 35 kg/m^2 with 1 or more obesity-related comorbidities including, but not limited to, T2DM, hypertension, hyperlipidemia, obstructive sleep apnea, asthma, severe urinary incontinence, and debilitating arthritis; or (3) BMI 30 to 34.9 kg/m^2 with diabetes or metabolic syndrome.[25] These procedures have shown major benefits to health, survival and quality of life, primarily through its impressive weight loss outcomes reporting reductions as great as 30-40 kg.[66] Of note, bariatric procedures will affect drug absorption either through pH or surface area available for absorption.[67] For people with diabetes, insulin and insulin secretagogue doses should be adjusted to minimize risk of hypoglycemia. Metformin, however, can be continued at preoperative doses.[64] While the complete effects of bariatric surgery on diabetes are yet to be elucidated, reports have indicated the remission of T2DM following surgery.[66] Improvements in various chronic health conditions and CVD risk factors have been described including diabetes, hypertension, resolution of hyperinsulinemia and hypertriglyceridemia.[63, 68-71]

Still, diabetes educators should express to peoples with diabetes that this procedure requires lifelong counseling, monitoring, and nutrient supplementation, to achieve and maintain weight loss and prevent nutritional deficiencies or a relapse into diabetes.[72]

Conclusion

Diabetes educators should address obesity as a component of diabetes self-management with the goal of empowering people with diabetes to adopt appropriate lifestyle changes. The most effective behavioral weight loss treatment is in-person, high-intensity (i.e., ≥14 sessions in 6 months) comprehensive weight loss interventions provided in individual or group sessions.52 A brief list of recommendations within this advisory has been composed to help guide the diabetes educator during such counseling of the obese person to manage or prevent diabetes.

- Establish a positive patient-centered partnership using non-judgmental bias, empathetic communication, and counseling strategies

- Discuss factors influencing body weight and individualize nutrition-related, physical activity and weight management goals
- Discuss weight loss treatment options
- Communicate with physicians to consider diabetes medications that are weight neutral or may favorably impact weight loss
- Create a support system by communicating with physicians and other practitioners to encourage and support lifestyle change in obese persons with or at risk for diabetes.
- Refer to community resources and programs for obtaining affordable, healthy food and beverages and opportunities for physical activity.
- Promote strategies for healthy coping to overcome barriers affecting goal attainment.

Acknowledgements:

Patricia Davidson DCN, RDN, CDE, LDN, FAND; Katherine O'Neal PharmD, MBA, BCACP, CDE, BC-ADM, AE-C; Lindsey Thurmes McCoy, RD, LD

References:

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015 2016. *NCHS Data Brief.* 2017(288):1-8.
2. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. *Jama.* 2016;315(21):2284-2291.
3. Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and Severe Obesity Forecasts Through 2030. *American Journal of Preventive Medicine.2012;* 42(6):563-570.
4. Amati F, Pennant M, Azuma K, et al. Lower thigh subcutaneous and higher visceral abdominal adipose tissue content both contribute to insulin resistance. *Obesity*. 2012;20:1115-1117.
5. Tremmel M, Gerdtham U, Nilsson P, et al. Economic burden of obesity: A systematic literature review. *Int J Environ Res Public Health*. 2017;14(4):435.
6. Recio-Rodriguez JL, Gomez-Marcos MA, Patino-Alonso MC. Abdominal obesity vs general obesity for identifying arterial stiffness, subclinical atherosclerosis and wave reflection in healthy, diabetics, and hypertensive. *BMC Cardiovasc Disord*. 2012;12:3.
7. Padula W, Allen R, Nair K. Determining the cost of obesity and its common comorbidities from a commercial claims database. *Clinical Obesity*. 2014;53-58.
8. Wander PL, Boyko EJ, Leonetti DL, et al. Change in visceral adiposity independently predicts a greater risk of developing type 2 diabetes over 10 years in Japanese Americans. *Diabetes Care*. 2012;36(2):289-293.
9. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
10. Leung M, Carlsson N, Colditz G, et al. The burden of obesity on diabetes in the United States: Medical expenditure panel survey, 2008-2012. *Value in Health*. 2017;77-84.
11. Slagter S, van Vliet-Ostaptchouk J, van Beek A, et al. Health-related quality of life in relation to obesity grade, type 2 diabetes, metabolic syndrome and inflammation. *PLOS One*. 2015. https://doi.org/10.1371/journal.pone.0140599.
12. Franz MJ, Boucher JL, Evert AB. Evidence-based diabetes nutrition therapy recommendations are effective: the key is individualization. *Diabetes Metab Syndr Obes*. 2014;7:65-72.
13. Dugan, JA. Exercise recommendations for patients with type 2 diabetes. *Journal of the American Academy of Physician Assistants*. 2016;29(1):13-18.
14. Chapman, C., Benedict, C., Brooks, S., & Schiöth, H. Lifestyle determinants of the drive to eat: A meta-analysis. *The American Journal of Clinical Nutrition*. 2012; 2 96(3), 492-7.
15. Yu JH, Kim MS. Molecular Mechanisms of Appetite Regulation. *Diabetes Metab J*. 2012 Dec;36(6):391-398. .
16. Feng, Helin, Zheng, Lihua, Feng, Zhangying, Zhao, Yaheng, & Zhang, Ning. The role of leptin in obesity and the potential for leptin replacement therapy. *Endocrine*. 2013;44(1), 33-39.
17. Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. Nutr Diabetes. 2012;2(1):e26.
18. Erion KA, Corkey BE. Hyperinsulinemia: a cause of obesity? *Curr Obes Rep*. 2017;6(2)178-186.

19. Upadhyaya S, Banerjee G. Type 2 diabetes and gut microbiome: At the intersection of known and unknown. *Gut Microbes*. 2015;6(2):85-92.

20. Le Chatelier E, Nielsen T, Qin J, Prifti E et al. Richness of human gut microbiome correlates with metabolic markers. *Nature.* 2013;500:541-546.

21. Fang S and Evans RM. Wealth management in the gut. *Nature.* 2013;500:538-539.

22. Komaroff, AL. The Microbiome and Risk for Obesity and Diabetes. *JAMA* 2017;317(4): 355–356., doi:10.1001/jama.2016.20099.

23. Jackson M, Goodrich J, Maxan M et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut*. 2015;65(5):749-756.

24. Modi, Sheetal R., et al. Antibiotics and the gut microbiota. *Journal of Clinical Investigation*. 2014;124(10):4212–4218.

25. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity – Executive Summary. 2016. DOI:10.4158/EP161365.GL.

26. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2017.

27. Moore JX, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Prev Chronic Dis*. 2017;14:160287.

28. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *Journal of the American College of Cardiology*. 2012;59(7):635-43.

29. Ali MK, Echouffo-Tcheugui J, Williamson DF. How effective were lifestyle interventions in real-world settings that were modeled on the Diabetes Prevention Program? *Health Aff* (Millwood). 2012;31(1):67-75.

30. Lindstr¨om J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet.* 2006;368:1673–1679.

31. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet.* 2008; 371:1783–1789

32. Knowler WC, Fowler SE, Hamman RF, et al.;Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374:1677–1686.

33. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

34. Fedewa MV, Gist NH, Evans EM, Dishman RK. Exercise and insulin resistance in youth: a meta-analysis. *Pediatrics.* 2014;133(1):e163-174.

35. Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children: A randomized controlled trial. *JAMA.* 2012;308(11):1103-1112.

36. US Dept of Health and Human Services. Managing Overweight and Obesity in Adults. Systematic Evidence Review from the Obesity Expert Panel. 2013.

37. American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Executive Summary: Guidelines for the management of overweight and obesity in adults. *Obesity*. 2013;22(2):S5-S39.

38. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet*. 2015;115(9):1447-63.

39. Wilding JP. The importance of weight management in type 2 diabetes. *Int J Clin Pract*. 2014;68(6):682-692.

40. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Archives of internal medicine.* 2010;170(17):1566-1575.

41. Redmon JB, Bertoni AG, Connelly S, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care.* 2010;33(6):1153-1158.

42. Fallah-Fini S, Adam A, Cheskin LJ, Bartsch SM, Lee BY. The additional costs and health effects of a patient having overweight or obesity: A computational model. *Obesity*. 2017;25:1809-1815.

43. Powers M, Bardsley J, Cypress M, et al. Diabetes self-management education and support in type 2 diabetes. *The Diabetes Educator*. 2017;43(1):40-53.

44. American Association of Diabetes Educators. AADE7™ self care behaviors. American Diabetes Educators Association. 2014. Available at: https://www.diabeteseducator.org/docs/default-source/legacy-docs/_resources/pdf/publications/aade7_position_statement_final.pdf?sfvrsn=4. Accessed May 23, 2018.

45. Calancie L, Leeman J, Jilcott Pitts SB, Khan LK, Fleischhacker S, Evenson KR, et al. Nutrition-Related Policy and Environmental Strategies to Prevent Obesity in Rural Communities: A Systematic Review of the Literature, 2002–2013. *Prev Chronic Dis*. 2015;12:140540.

46. Haas L, Maryniuk M, Beck J, et al. National standards for diabetes self-management education and support. *Diabetes Care.* 2013;36 Suppl 1:S100-108.

47. Aade. AADE Guidelines for the Practice of Diabetes Self-Management Education and Training 2017. *Diabetes Care*. 2017;40(10):1409-1419.

48. Evert AB, Boucher JL, Cypress M, et al. Nutrition Therapy Recommendations for the Management of Adults With Diabetes. *Diabetes Care.* 2013;36(11):3821-3842.

49. Academy of Nutrition and Dietetics. Adult Weight Mangagement Guideline (2014) Chicago: Academy of Nutrition and Dietetics (AND) Evidence Analysis Library. http://andevidencelibrary.com. Accessed August, 2018

50. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Medicine and science in sports and exercise.* 2009;41(2):459-471.

51. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans Available at: http://www.health.gov/paguidelines/. Accessed Feb. 22, 2018.

52. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2014;129(25 Suppl 2):S102-138.

53. Kenkre J, Tan T, Bloom S. Treating the obese diabetic. *Expert review of clinical pharmacology.* 2013;6(2):171-183.

54. Soeliman F and Azadbakht L. Weight loss maintenance: A review on dietary related strategies. *Journal of Research in Medical Sciences, 2014;19* (3):268-275.

55. Brantley, P.J., Stewart, D.W., Myers, V.H. et al. Psycosocial predictors of weight regain the weight loss maintenance trial. *J Behav Med*, 2014 37: 1155. https://doi-org.proxy-wcupa.klnpa.org/10.1007/s10865-014-9565-6

56. American Diabetes Association. Psychosocial Care for people with diabetes: A position statement of the American Diabetes Association. *Diabetes Care. 2016;* 39:2126-2140.

57. American Diabetes Association. Obesity management for the treatment of type 2 diabetes: Standards of Medical Care in Diabetes 2018. *Diabetes Care*. 2018;41(Suppl. 1): S65–S72.

58. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surg Obes Relat Dis.* 2013; 9(2):159-191.

59. Medici V, McClave S, and Miller A. Common Medications Which Lead to Unintended Alterations in Weight Gain or Organ Lipotoxicity. *Current Gastroenterology Reports,* 2016; *18*(1):1-12.

60. Yanovski SZ and Yanovski JA.Long-term drug treatment for obesity a systematic and clinical review. *JAMA*. 2014;311(1):74-86.

61. Henry RR, Chilton R, and Garvey WT. New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). *Journal of Diabetes and Its Complications,* 2013; *27*(5): 508-18.

62. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes, Obesity & Metabolism.* 2013;15(4):372-382.

63. Franz M, MacLeod J, Evert A, Brown C, and et al. Academy of Nutrition and Dietetics Nutrition Practice Guideline for Type 1 and Type 2 Diabetes in Adults: Systematic Review of Evidence for Medical Nutrition Therapy Effectiveness and Recommendations for Integration into the Nutrition Care Process. *Journal of the* Academy *of Nutrition and Dietetics*. 2017; 117.

64. WCI N. Prescription Medication for the Treatment of Obesity.Available at: http://win.niddk.nih.gov/publications/prescription.htm.

65. Maggard-Gibbons M, Maglione M, Livhits M, and et al. Bariatric Surgery for Weight Loss and Glycemic Control in Nonmorbidly Obese Adults With DiabetesA Systematic Review. *JAMA.* 2013;309(21):2250–2261.

66. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med.* 2012;366(17):1567-1576.

67. Edwards A, Ensom MH. Pharmacokinetic effects of bariatric surgery. *The Annals of pharmacotherapy.* 2012;46(1):130-136.

68. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. *Heart (British Cardiac Society).* 2012;98(24):1763-1777.

69. Vest AR, Heneghan HM, Schauer PR, Young JB. Surgical management of obesity and the relationship to cardiovascular disease. *Circulation.* 2013;127(8):945-959.

70. Priester T, Ault TG, Davidson L, et al. Coronary calcium scores 6 years after bariatric surgery. *Obes Surg.* 2015;25(1):90-96.

71. Erion KA, Corkey BE. Hyperinsulinemia: a cause of obesity? *Curr Obes Rep*. 2017;6(2):178-186.

72. Ikramuddin, S., Korner, J., Lee, W., Thomas, A., Connett, J., Bantle, J., . . . Billington, C.Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A1c, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study. *JAMA, 2018; 319*(3), 266-278.

