CME OUTFITTERS

# Clinical Pathways in T2D Care

## Overcoming Inertia, Implementing Innovation

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## Introduction

Controlling hyperglycemia and preventing or mitigating chronic complications are key goals of diabetes management, yet the major focus of endocrinologists is A1C reduction, sometimes to the exclusion of other risk factors or conditions. In fact, nearly 90% of individuals with type 2 diabetes (T2D) have overweight or obesity—which is one of the most potent risk factors for T2D. There is strong evidence that obesity management can delay progression from prediabetes to T2D and may be beneficial in treating T2D.

This is a transformational era, in terms of the tools available to treat type 2 diabetes (T2D) and obesity in ways that can benefit patients. Long-acting analogues of the naturally occurring incretin, glucagon-like peptide-1 (GLP-1), and those modified to interact also with receptors for glucose-dependent insulinotropic polypeptide (GIP) have shown high glucose-lowering and weight-lowering efficacy when administered by once-weekly subcutaneous (SC) injection. These analogues introduce a new peptide-based therapy paradigm for T2D and obesity, yet many endocrinologists are not up to date with the latest developments and guidelines, including the 2023 Update of the American Association of Clinical Endocrinology (AACE) Consensus Statement Algorithm on Comprehensive T2D Management.

Both patient and clinician factors can impede the prompt and proper use of new medications leading to therapeutic inertia, including poor adherence to therapies by the individual being cared for, poor recognition of the needs of patients by clinicians, and barriers at the health system level. Therapeutic inertia is quite common and affects nearly half of all patients with T2D. Addressing it is a priority for reducing the burden of T2D and its complications.

To address these practice gaps, CME Outfitters conducted a 2-day educational activity, moderated

by Timothy Garvey, MD (University of Alabama at Birmingham, Birmingham, AL) and designed to train and update endocrinology fellows, as well as a national audience of endocrinologists, on the expanding armamentarium of therapies for T2D that have efficacy for obesity, cardiovascular disease (CVD), and other comorbid conditions on avoiding therapeutic inertia through implementing the latest practice guidelines on treatment selection and intensification. The following article is a summary of the presentations, highlighting the key messages and clinical takeaways.

## Obesity as a chronic and genetic disease

A "diabetes belt" was identified by the Centers for Disease Control and Prevention (CDC), based on counties with the highest prevalence of diabetes.[3] This area includes the Appalachian counties and the Southern tier of counties. Further, there is a co-localization of metabolic and vascular disease across the United States (US) of diabetes and obesity, heart disease, and stroke.

Obesity is a two-step disease in which disordered regulation of caloric intake results in high levels of adiposity, then high levels of adiposity impair health via weight-related complications. The determinants of body weight are very complex and vary from individual to individual. Numerous organizations vary in the precise definition of obesity, but all share similar concepts. AACE and the European Association for the Study of Obesity (EASO) refer to obesity as an "adiposity-based chronic disease (ABCD)," the World Obesity Foundation defines obesity as "a chronic, relapsing, progressive disease," and The Obesity Society, "a multi-causal chronic disease that, over time, leads to structural abnormalities, physiologic derangement, and functional impairments." Genome-wide association study (GWAS) studies have identified over a hundred susceptibility genes for obesity.[5] These genes interact with environmental factors. Food availability, built environments, and socioeconomic status interact with behavior, cultural, and personal preferences for diet and physical activity, as well as other biological factors, such as the in-utero environment, birth weight, gender, age, and other diseases. This complex interaction sets the degree of adiposity for a particular individual. However, heritability should not define a person's destiny, even though genetics do play a pivotal role.

Treating people begins with stratifying and characterizing people based upon BMI and degree of impaired health. The AACE Obesity Guidelines propose a simple clinically-intuitive system: stage 0 represents ABCD with no complications, stage 1 represents the presence of mild to moderate complications, and stage 3 the presence of at least one severe complication. The Edmonton Obesity Staging System (EOSS) characterizes people based upon comorbid health conditions and functional and emotional and psychological impairments.[4,6,7] At stage zero, a person may have some obesity, but is otherwise well and without associated complications or impairment in function and normal metabolic labs and vitals. Conversely, at stage 4 a person might have obesity and associated weight-related comorbidities in other impairments, such as T2D, severe depression, or being house-bound.

A treatment plan consisting of nutrition, physical activity, sleep hygiene, and other general health factors. Unfortunately, healthcare professionals are not engaging their patients in a conversation about their weight.[9] In a survey of 3,000 people with obesity, 71% said that their practitioner discussed weight within the past five years and 55% said they were diagnosed with obesity, but only a quarter of them said that there was any kind of scheduled follow-up or telephone call after the last visit. Healthcare practitioners cited the reasons for which they were not discussing weight that included lack of essential or adequate time (52%), more important issues to discuss (45%), and belief that the

patient did not want to or was not motivated to lose weight (53%). It was unclear if that belief was founded on fact or in bias.

## PATHOPHYSIOLOGY OF WEIGHT GAIN

Obesity affects the interaction between satiety factors and feeding centers in the brain and the regulation of body weight.[11] This begins with a number of hormones that derive from peripheral tissues, largely the gut: ghrelin from stomach, leptin from fat, CCK, GLP-1, PYY from intestines, and amylin insulin and pancreatic polypeptide from the pancreas (Box 1).[8] These factors are released into

**Box 1.** Hormones involved with satiety

Eating is a complex activity that involves many hormones regulating hunger and satiety.

- Ghrelin and leptin create a highly interactive and precise satiety regulatory system.[1] Ghrelin stimulates the orexigenic pathway that increases appetite. Ghrelin binds its cognate receptor on the surface of neuropeptide Y (NPY)-secreting neurons, causing a release of NPY as a neurotransmitter that activates neurons upstream in the paraventricular nucleus on up to higher cortical centers. Leptin binds its receptor on pro-opiomelanocortin (POMC) neurons, activating POMC cleavage and αMSH production and the anorexigenic pathway that decreases appetite, but also activating receptors on NPY-secreting neurons that inhibit the orexigenic pathway.
- Tissue-specific processing of preproglucagon leads to the production of different sets of satiety hormones. In pancreatic α cells, preproglucagon is cleaved by Psck2 to glucagon, glicentin-related pancreatic peptide (GRPP), and other peptides, while in the brain and GI system, Psck1/3 cleaves preproglucagon to GLP-1, GLP-2, oxyntomodulin, and glicentin.[2]
- Additional factors come from endothelial endocrine (enteroendocrine) cells of the gut specialized to secrete specific satiety factors.[8] For example, L cells in the distal intestine and colon will produce GLP-1, GLP-2, and PYY; I cells in the proximal intestine secrete CCK; K cells from the proximal intestine release GIP. These factors also regulate motility and other functions of the GI system.
- The pancreatic polypeptide genes are a highly related family.[10] Neurotransmitter NPY binds to the Y1R and Y5R receptors in the hypothalamus and activates the orexigenic pathway to increase appetite and delay satiety. Peptide tyrosine tyrosine (PYY) is produced by L cells in the distal intestine and stimulates αMSH production from POMC neurons. PYY is a satiety factor that interacts with vagal nerve input into the nucleus tractus solitarius and regulates the GI system through reducing gastric motility and emptying. Pancreatic polypeptide, on the other hand, is produced in pancreatic islets and binds a wider range of receptors, though strongly to Y4R. It also reduces appetite, regulates the GI tract, inhibits pancreatic exocrine secretion, gallbladder contraction, and gut motility.
- POMC is processed in the hypothalamus by Pcsk1 to adrenocorticotropic hormone (ACTH), which is involved in the stress response. Pcks2 further processes ACTH to αMSH, which is critical in the anorexigenic pathway. Other factors derived from pro-opiomelanocortin, include βMSH, and lipotropin.

the bloodstream and interact with pro-opiomelanocortin (POMC) neurons and neuropeptide Y (NPY)-secreting neurons in the arcuate nucleus of the hypothalamus to increase or decrease activity of the anorexigenic and orexigenic pathways.

In patients with obesity, these regulatory systems are set to generate increased adiposity and to sustain higher levels of adiposity as part of the pathophysiology of this disease. In this regard, the hypothalamus is central to weight regulation, though the entire brain affects eating and weight regulation, such as:

- Serotonergic neurons in the mesolimbic system that mediate emotional eating.
- Dopamine neurons that are involved in reward and hedonistic eating.
- Stimulation of eating from the olfactory bulb and taste systems.
- The cerebral cortex with its executive function that adds a layer of intent to eating.

### OBESITY PROTECTS OBESITY: MALADAPTATIONS IN WEIGHT REGULATION

The pathophysiological root of obesity involves regulation of energy intake and energy balance. In obese patients who are able to attain a weight loss, orexigenic hormones (e.g., ghrelin) increase, creating a desire to eat more, while anorexigenic hormones (e.g., PYY, CCK, amylin) decrease. Resting energy expenditure decreases simultaneously while the patient becomes hungrier for more calorie-dense foods. These observations support the set point theory for obesity, and explain why patients regain weight after a lifestyle intervention.[12,13]

Obesity can affect almost every system in the body and a person's quality of life, much the same way other chronic diseases affect people. Internalized weight bias and stigmatization impairs quality of life, can engender kind of a sense of impaired self-efficacy in patients, and reduce the efficacy of your therapeutic program. It is important to recognize the psychological overlay of the disease that includes increased levels of anxiety, stress, depression, and eating in some patients. Biomechanical complications compound the metabolic dysfunction due to carrying around increased body mass over a period of time, including sleep apnea, asthma, osteoarthritis, immobility, GERD, stress, and incontinence. Of course, cardiometabolic complications are well known.

## Development of insulin resistance

BMI, as a general measure of adiposity, only explains 11% of the variability in insulin sensitivity.[14] Insulin resistance and what generates increased adiposity segregate independently, but they interact with each other because obesity can exacerbate insulin resistance. There are individuals who are obese and insulin sensitive and individuals who are lean and insulin resistant, giving rise to the notion of a metabolically healthy obese person.

From the ARIC study, BMI has relatively small impact on T2DM risk in insulin sensitive individuals, while having a larger impact on T2DM risk in insulin resistant individuals.[15] In this 20-year study, survival was increased and congestive heart disease (CHD) was decreased in metabolically healthy individuals, regardless of weight.

More important than BMI is the location of the fat. Intraabdominal fat, rather than general adiposity, is associated with insulin resistance regardless of BMI.[16] Fat in the intraabdominal compartment,

particularly if in an insulin resistant background, results in adipose tissue inflammation and influx of macrophages, crosstalk between macrophages in an adipose tissue, and dysregulated secretion of adipocytes factors, which contribute to the metabolic syndrome and vascular sequelae of cardiometabolic disease.

## UPDATED UNDERSTANDING OF HYPERGLYCEMIA IN T2D

The classic view of hyperglycemia was the result of insulin resistance in liver and muscle and impaired insulin secretion from the pancreas. The updated understanding of hyperglycemia brings in adipose tissue into the equation because this tissue secretes cytokines and free fatty acids while decreasing adiponectin.[17] The resulting glucose toxicity, lipotoxicity, and inflammation impairs insulin secretion, inducing insulin resistance in peripheral organs and leading to hyperglycemia. This leads to a vicious cycle of hyperglycemia producing more hyperglycemia.

## NEED FOR NEW DIABETES MEDICATIONS

It is important to prevent progression from the insulin resistant state to more overt disease, including diabetes.[17] For many years, and perhaps over the lifetime in some individuals, a decrease in insulin sensitivity or insulin resistance is matched by increases in insulin secretion, whether it's first phase or late phase. Over time, glucose toxicity and lipotoxicity lead to impaired beta cell function. In the pre-diabetic state, a falloff in first phase insulin secretion gives rise to an increase in postprandial glucose. Fasting glucose levels and decreased late-phase insulin secretion follow before the onset of overt diabetes.

In the GRADE trial funded by NIH, patients with diabetes who failed metformin were then randomized to four different medicines: a sulfonylurea, glimepiride; a DPP-4 inhibitor, sitagliptin; a GLP-1 receptor agonist, liraglutide; or glargine insulin.[18] Over a five-year period, none of these medicines maintained a low hemoglobin A1C well and led to adequate outcomes. None of these medications were able to prevent worsening of the patient's diabetes. As a result, there continues to be a need for medicines that are going to help patients achieve their target hemoglobin A1C and keep the hemoglobin A1C down over the course of the disease.

## COMPREHENSIVE CARE OF PATIENTS WITH T2D WITHIN THE CONTEXT OF CARDIOMETABOLIC DISEASE

Insulin resistance is a systemic metabolic, vascular, and inflammatory process. Inflammation, oxidative stress, impaired substrate oxidation, endothelial dysfunction, vascular reactivity, changes in lipoproteins, increased free fatty acids, dysfunctional adipose tissue, and ectopic fat in multiple organs (muscle, liver, heart, pancreas) contribute to insulin resistance.

Early in the progression to cardiometabolic disease state, it is unclear if the glucose regulatory defect produces the inflammation or the inflammation that produces the insulin resistance. Subclinical insulin resistance may begin in childhood and extend over most of some individual's lifetimes. However, in many individuals, it will eventually give rise to clinically identifiable states of progressive disease in the spectrum of cardiometabolic disease, whether it's prediabetes, metabolic syndrome, the dyslipidemia, pre-hypertension, ventral adiposity, or hepatic steatosis.[19] Unrecognized and untreated, these patients are at risk of progressing to end stage manifestations of cardiometabolic disease,

including atherosclerotic events, congestive heart failure, type two diabetes, NASH, hypertension, and renal dysfunction.

Given the association of inflammation and adipose tissue with the insulin resistant state, there is a need for a more holistic model of treatment that includes both hemoglobin A1C and obesity. Ideally, this approach would have a strong preventative aspect to hinder the progression to end-stage manifestations. Opportunities for prevention occur at each stage of disease progression, with treatment becoming increasingly aggressive as patients approach or attain end-stage manifestations. In this regard, treating obesity early can significantly help patients avoid worsening outcomes.

## Incretin effect as a target for treatment of diabetes and obesity

Multiple metabolic abnormalities are associated with T2D, famously grouped in the "ominous octet."[20] The eight dysfunctions identified by DeFronzo are comprised of muscle, liver, and brain insulin resistance, pancreatic β-cell failure, accelerated lipolysis in adipose tissue, pancreatic α-cell-mediated hyperglucagonemia, increased glucose reabsorption by the kidneys, and decreased incretin effect in the GI tract. Each of these defects contributes to hyperglycemia. Some of these phenomena are primary, and precede and predict diabetes, such as insulin resistance and β-cell dysfunction. Some abnormalities are secondary to worsening metabolic dysfunction, such as hepatic glucose production, renal glucose reabsorption, and glucagon over-secretion. The incretin defect may be one of the more primary defects, because it represents abnormalities in β-cell dysfunction. It is important to remember that this is a dynamic process, so the condition and needs of patients change over time.

### THE INCRETIN EFFECT

The incretin effect describes the contribution of the gut to glucose homeostasis.[21] While 2 glucose challenge tests in an individual—one oral and intravenous—can be matched to produce the same increase in plasma glucose levels, insulin secretion will be significantly higher in the oral test.

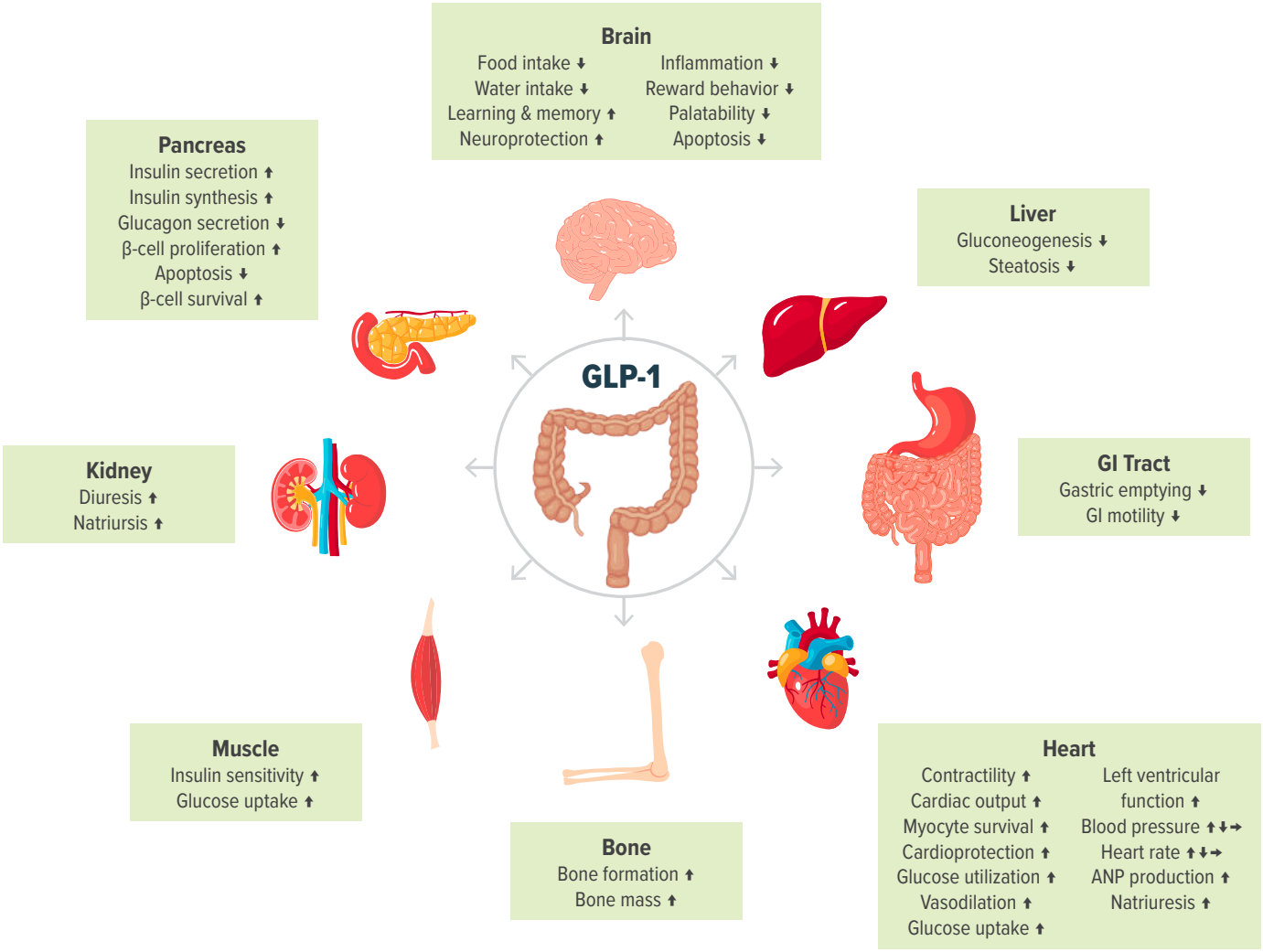
Two incretin hormones, GIP and GLP-1 are primarily responsible for this effect. Both circulate at very low levels in the fasting state and are secreted rapidly after ingestion of a glucose challenge or any food challenge. Although this effect was first observed with glucose, fat is the strongest secretagogue for GIP. These endocrine hormones are produced by different cells: L cells produce GLP-1 and K cells produce GIP.

GLP-1 is a 30/31-amino acid peptide cleavage product from preproglucagon in specialized endocrine L-cells located in the distal intestinal mucosa.[2,4] GIP is a 42-amino acid peptide, belongs to the same family of proteins, and is cleaved from a 153-amino acid precursor. Both GLP-1 and GIP are released from the gut in response to nutrient intake—primarily glucose and fat. GIP is synthesized in K-cells located in the proximal intestinal mucosa.

After secretion, GIP-1 and GIP engage with canonical receptors on target tissues. A transmembrane G protein-coupled receptor increases adenylyl cyclase activity and produces increased cyclic AMP which downstream, through PKA and EPAC, results in calcium influx and closing of potassium channels that in turn result in insulin secretion.[22] The activation of insulin secretion is glucose dependent.

In addition to the effects in the pancreas, GLP-1 has direct effects throughout the body (Figure 1).[22]

**Figure 1.** Multiple GLP-1 bioeffects reflect expression of GLP-1 receptors in multiple tissues




There is a natriuretic effect in the kidneys. In immune cells and vascular system, it seems to decrease inflammation. And in the α-cells, it decreases glucagon secretion. In the brain, there are effects on food intake, probably effects on neuroprotection as well. And it also has direct effects on the gut, including reduction of lipoprotein secretion, especially postprandially. Indirect effects are found in the liver (reduced hepatic glucose output), adipocytes (reduced lipogenesis), and possibly on other cell types to increase insulin sensitivity and glucose utilization.

GIP has overlapping but non-identical effects and enhances insulin biosynthesis and secretion from β-cells.[22] GIP increases glucagon synthesis, possibly lipogenesis, and may have protective effects on the brain, heart, bone, and cardiovascular systems.

Both GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase 4 (DPP-4)—within minutes.[23] DPP-4 is ubiquitous on endothelial cell surfaces and in the circulation and cleaves the n-terminal 2 amino acids from these incretins.

## INCRETIN RESPONSE DEFECT IN PATIENTS WITH T2D

The incretin response in patients with diabetes is markedly decreased, compared to patients without diabetes.[21,24] The minimal differences in GLP-1 and GIP expression between these patient populations cannot explain the differences in response. Instead, the insulin response to GLP-1 is impaired in T2D but can be reached at supraphysiologic levels of GLP-1. In fact, GLP-1 infusion into patients with T2D temporarily enhances insulin secretion and reduces glucagon secretion and glucose levels can be normalized.[25,26] After normalization of glucose levels, insulin and glucagon levels return to normal. These results are primarily responsible for the development of drugs that focused on GLP-1 rather than GIP.

## RATIONALE FOR GLP-1 RECEPTOR AGONISTS

Incretins play a key and early role in maintaining glucose homeostasis, which is diminished in patients with T2D. Incretins target multiple metabolic defects of T2D, including those not addressed by traditional medications. These defects include impaired insulin secretion, decreased incretin effect, decreased glucose uptake or insulin resistance, increased glucagon secretion, increased hepatic glucose production, and possibly neural abnormalities. Importantly, incretins do not cause hypoglycemia and are favorable effects on weight. There are two classes of agents that work through the incretin system: DPP-4 inhibitors and GLP-1 receptor agonists.

## DPP-4 INHIBITORS

DPP-4 inhibitors block GIP and GLP-1 degradation, both in response to a meal and in the intervening stages.[27] These are associated with increases in insulin secretion, decreases in glucagon, and overall improved glucose tolerance. Agents in this class include alogliptin, saxagliptin, sitagliptin, linagliptin, and vildagliptin. These agents are all very well-tolerated, once-daily, and very effective at inhibiting DPP-4. They all have the same efficacy, which is an A1C reduction of approximately 0.6-0.7%, similar to a suflonylurea.[28-32] While people gain weight on the sulfonylureas, they lose weight on the DPP-4 inhibitors when combined with metformin—approximately a kilogram—and the rates of hypoglycemia are much less (1%-5% vs. 23%-38%). However, they are still expensive and there is a warning for pancreatitis.

## GLP-1 RECEPTOR ANALOGS

The GLP-1 receptor analogs are also peptides, and for the most part, given by injection, with one exception. There are two classes, human GLP-1-based therapies, and excedin-4-based therapies (Figure 2). The former agents include albiglutide, dulagutide, liraglutide, and semaglutide (injectable and oral). The latter agents include exenatide and a long-acting version, lixisenatide, tirzepatide, and efpeglenatide, which has not been released in the U.S.

Major differences exist among GLP-1 receptor agonists. Exenatide and lixisenatide are approximately 50% homologous to human GLP-1. These are relatively small polypeptides. On the other hand, liraglutide, dulaglutide, semaglutide, albiglutide are all approximately 90% homologous. Liraglutide and semaglutide are relatively small fatty acid-conjugated polypeptides, but dulaglutide and efpeglenatide have been complexed to IgG Fc domain and albiglutide to albumin.

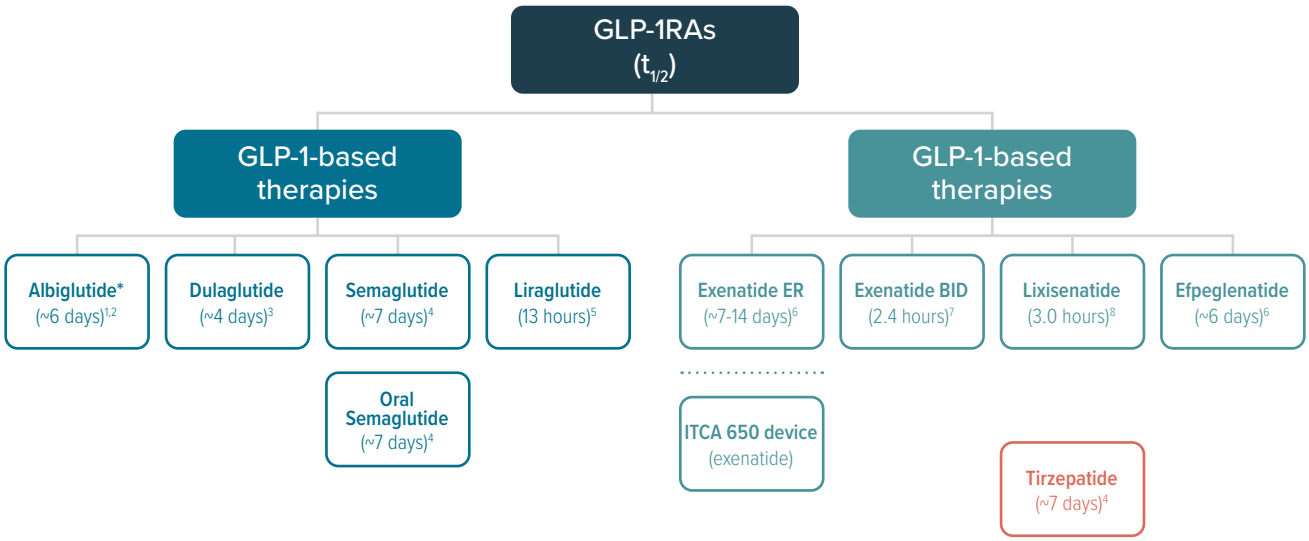
As figure 2 indicates, these drugs differ in their half-life. Short versus long-acting indicates whether

or not they have coverage for more than 12 hours that provide reductions in fasting glucose levels. In a comparison of lixisenatide vs. liraglutide, longer-acting liraglutide reduces glucose excursion at breakfast, lunch, and dinner, and overall reduces fasting glucose levels.[33] In contrast, shorter-acting lixisenatide effectively abolishes the prandial peak with breakfast but has minimal effect with lunch or dinner. These effects translate into improved A1C efficacy in this 28-day study versus the shorter-acting GLP-1 agonist and much better changes in fasting glucose. A similar effect of half-life was seen in a comparison of twice-daily and once-weekly exenatide.[34]

**Figure 2.** GLP-1RA landscape 2023

$t_{1/2}$ depicts agent half live. *Albiglutide was withdrawn from market July 2018

BID, twice daily; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist





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The main function of short-acting GLP-1RAs is in decreasing postprandial glucose, with lesser impact on fasting glucose, while the long-acting GLP-1 agonists are more effective at decreasing fasting glucose and less impact on postprandial glucose.[35] This is an important distinction, as lower fasting glucose levels translate into lower hemoglobin A1C levels. In the later studies with more potent GLP-1RAs, improved weight loss was seen.

To summarize the advantages and disadvantages of GLP-1 receptor agonists, they are similar in that they enhance insulin secretion, decrease glucagon in glucose-dependent manners, have a low risk of hypoglycemia, a quick onset of action, and superior hemoglobin A1C efficacy, in addition to providing weight loss and CVD benefit. But they are injections and expensive. While generally safe, some patients experience nausea associated with the use of these drugs, usually when they are starting or titrating the drugs. There are warnings about pancreatitis and medullary thyroid

carcinoma. And, significantly, there is a tremendous rebound effect coming off these agents. They are highly effective at suppressing hunger, and patients need to wean off these agents slowly, if they ever stop taking the medication.

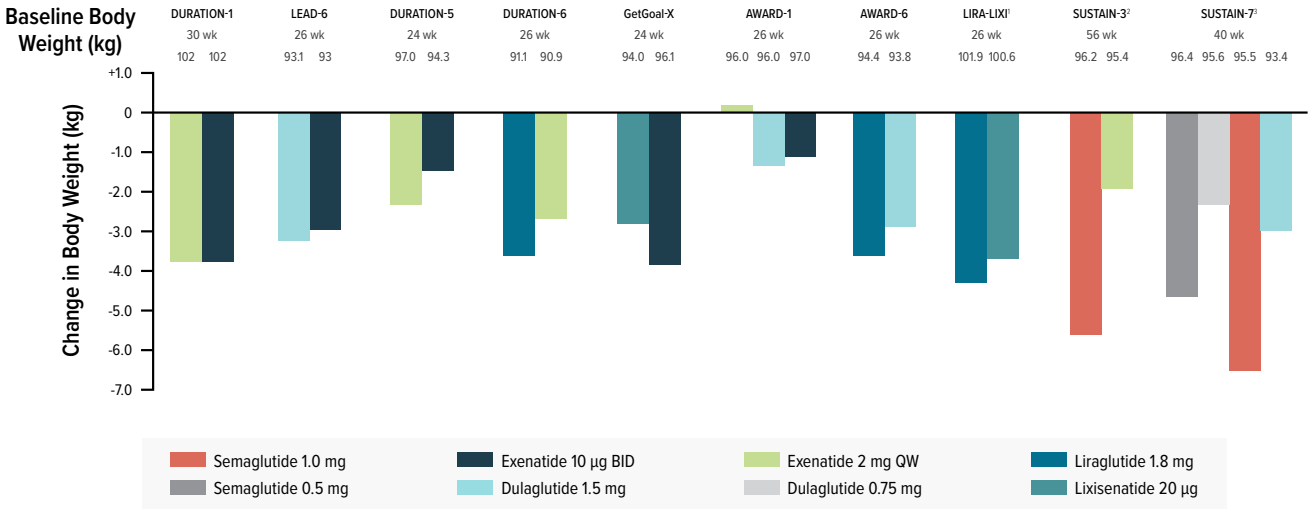
## Benefits of GLP-1 and GIP-GLP-1 receptor agonists beyond glycemic control

There are a number of GLP-1 receptor agonists approved for diabetes. They are highly effective at controlling hemoglobin A1c. Longer-acting agents are more effective in reducing fasting glucose and hemoglobin A1c levels. These agents also have benefits beyond glycemic control, including weight loss and CVD benefits. Patients that have diabetes and obesity have two different diseases. Both agents deserve effective therapy in order to improve overall health and quality of life.

### GLP-1RAS AND WEIGHT LOSS

With the GLP-1RAs, there is generally a decrease in hemoglobin A1C of 1%-2%, and this does not increase significantly at higher doses. The head to head trials of diabetes doses of liraglutide, dulaglitide, and semaglutide (1 mg/wk) demonstrate a change in body weight up to approximately 6%, on average, with longer-acting agonists providing a greater loss (Figure 3).[35]

**Figure 3.** Head-to-head trials of GLP-1 RAs: changes in weight





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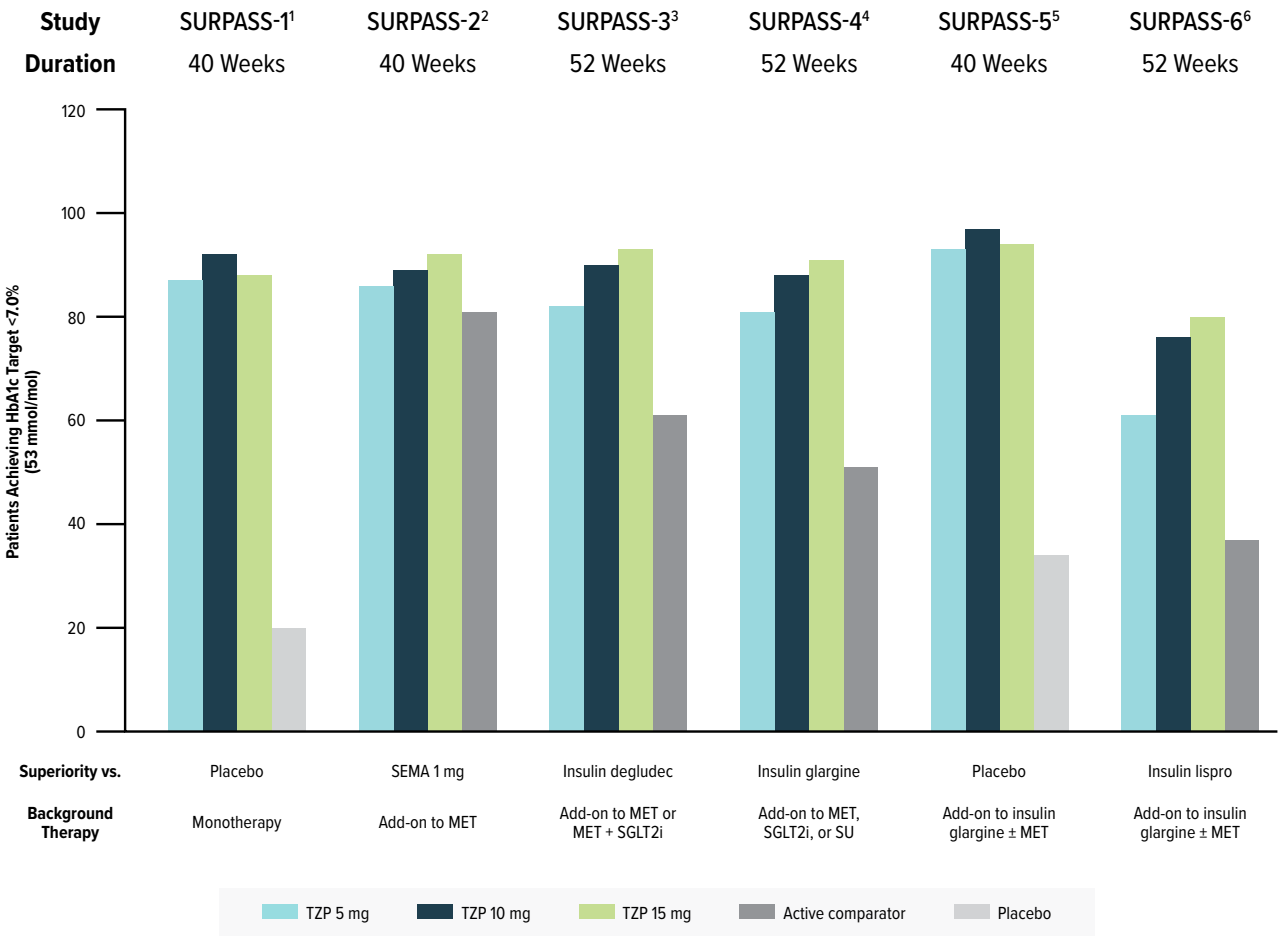
## DUAL GIP/GLP-1 RA FOR GLYCEMIC CONTROL

Tirzepatide is a 39 amino acid peptide GIP/GLP-1 RA engineered to bind to both GLP-1 and GIP receptors.[40] It includes a C20 fatty acid moiety that allows binding to albumin and providing a longer (~5 day) half-life. Plasma levels are not affected by hepatic or renal impairment, and it is administered as a once-weekly subcutaneous dose.

The SURPASS suite of trials were designed to evaluate this drug for treatment of diabetes.[41,42] Hemoglobin A1c was the primary outcome measure, and patients with a BMI ≥25 were included. A number of these SURPASS trials were carried out in the presence and absence of other diabetes drugs to assess its broad applicability in diabetes, both from monotherapy, to add-on to metformin, used with glargine, or more than one oral agent. In these trials, 90% of patients reached the ADA target of less than 7%, over 80% reaching the AACE target of equal or less than 6.5%, and at the top dose, over half the patients achieving a normal hemoglobin A1c without a significant incidence of severe hypoglycemia (Figure 4).[43-47]

**Figure 4.** SURPASS Trials: Proportion of Patients Achieving HbA1c < 7.0%





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For patients in the SURPASS trials with both obesity and diabetes, weight loss was approximately 11%, with approximately a quarter losing ≥15%, and almost half losing ≥10%, of their body weight.

## WEIGHT LOSS AS THE CENTRAL AXIS OF TREATMENT IN T2D

Obesity treatment is dependent on three major therapeutic modalities: medications, lifestyle and bariatric surgery.[48] With medications, patients lose weight because it inhibits your appetite, and that helps patients adhere to a reduced-calorie diet. And generally, we have to prescribe a reduced-calorie diet and the other components of lifestyle therapy, including exercise and behavioral modifications, to get maximal efficacy out of these medicines.

However, some of these new medicines are very powerful anorectic agents. It varies, but some patients just stop eating less than 1,000 calories a day, and their BMI keeps dropping. You can tell them to eat more, but sometimes they really can't do that. For these patients, the focus shifts to diet quality, because these patients are not getting enough protein and other nutrients, such as calcium, iron, and other micronutrients. It is unclear, but the vitamin replacement strategies and protocols in bariatric surgery might be applicable to second-generation obesity medicines.

Treatment of patients with obesity is aligned with reducing complications of the disease and improving quality of life, not losing a given amount of weight.[48] This is considered a complication-centric approach to care, and treating obesity as an "adiposity-based chronic disease (ABCD)."[49,50]Treatment of patients with obesity is aligned with reducing complications of the disease and improving quality of life, not losing a given amount of weight.[48] This is considered a complication-centric approach to care, and treating obesity as an "adiposity-based chronic disease (ABCD)."[49,50]

## GLP-1 AND DUAL GIP/GLP-1 RAS FOR WEIGHT LOSS

Standard weight loss medications include phentermine, a sympathomimetic amine, orlistat, the GI lipase inhibitor, topiramate, a GABA receptor modulator, naltrexone, a mu-opioid receptor antagonist, in combination with bupropion, a dopamine noradrenaline reuptake inhibitor. Liraglutide and semaglutide are approved for weight loss. Most recently tirzepatide was approved for the treatment of obesity.

In general, use of these agents result in weight loss and hemoglobin A1c reduction, but the hemoglobin A1c is going down with less need for conventional diabetes medicines. Patients tend to be hypocaloric very early on, and these patients may require dose reductions of insulin and sulfonylureas in order to avoid hypoglycemia. The hemoglobin A1C reaches it's lowest at around 20 weeks, but weight loss continues for over a year.

Tirzepatide is highly effective at reducing body weight in patients with T2D and obesity. In SURMOUNT-1, that enrolled patients with just obesity, weight loss over 72 weeks was 22.5%.[51] Nearly all patients lost ≥5%, 90% lost ≥10%, 75% lost ≥15%, and 40% lost ≥25% more of their body weight.

However, in SURMOUNT-2, the patients had both obesity and diabetes, and weight loss was 15.7%, which is the highest seen in patients with obesity and diabetes, but less than the weight loss in patients without diabetes in the SURMOUNT-1 study.[52] Over 80% of patients lost ≥5%, approximately two thirds lost ≥10%, over half lost ≥15%, and approximately a third lost ≥20%. Participants also reduced their BMI and waist circumference, and the majority achieved a hemoglobin A1C ≤6%. Importantly, hypoglycemia was ≤5% grade 2 and 0% grade 3.

Another important effect is that fasting insulin decreased 40%, while the fasting glucose decreased 50%.[52] In addition, patient lipid profiles and blood pressure improve significantly. This suggests that it is not the incretin effect that is lowering the hemoglobin A1C, it is the weight loss, and is indicative of a profound increase in insulin sensitivity in these patients. The side effects of tirzepatide are mostly GI related and include nausea, diarrhea, vomiting, constipation.

### OPPORTUNITIES FOR PRIMARY, SECONDARY, AND TERTIARY PREVENTION OF CARDIOMETABOLIC DISEASE

Obesity exacerbates the insulin-resistant state, leading to progression of cardiometabolic disease. A number of GLP-1 RAs have been tested in cardiovascular outcomes trials. Liraglutide, semaglutide, albiglutide, and dulaglutide have shown cardio-protection, with respect to MACE outcomes.[53] There's also a pretty good agreement in terms of them being renal-protective as well.

The LEADER trial was the first study that showed a cardio-protection with a GLP-1 receptor agonist (liraglutide) with a decrease in hazard ratio of about 13%. For semaglutide in the SUSTAIN 6 and PIONEER 6 studies, there were statistically significant less progression to MACE, with a decrease in hazard ratio of about 26%.[54] In the SELECT study, semaglutide was also cardio-protective in patients with simple obesity without diabetes.[55] The MACE primary composite outcome hazard ratio was 0.80 (95%CI 0.72-0.90) vs. placebo. Death from any cause was reduced by 20%. Semaglutide also appears to be protective against heart failure, NASH, and kidney damage and improves quality of life for patients with obesity.[56-58] Trials are pending with tirzepatide to look at these same endpoints.

## Deciphering the guidelines for management of T2D

Providing guideline-concordant care is critical to achieving optimal outcomes. Part of this is to ensure that patients understand their disease and treatment options. And another part is helping them to access the right medication for them. Too often, patients with limited financial means or low health literacy will not continue the treatment plan.

Clinical practice guidelines (CPGs) are recommendations that are provided by designated and recognized experts regarding the care of patients in specified conditions. Professional practice guidelines (PPGs), on the other hand, are more expansive in scope and often encompass aspects of diagnosis, evaluation, management, and treatment of a specific condition or state. PPGs provide guidance on optimal care, when care is not limited; CPGs provide guidance on practical care in less than ideal environments.

The current ACE guidelines have 11 distinct sections, and one of the most important points to be aware of is there's been a significant paradigm shift in the last few years from the old gluco-centric approach to a complication-centric approach (Figure 5).[59] In this view, attaining a low fasting glucose level is secondary to reducing complications of T2D and obesity. Clinicians need to have an accurate inventory of a patient's health, including comorbidities, and this needs to be updated at each visit.

### ADIPOSITY-BASED CHRONIC DISEASES (ABCD)

Beginning with obesity, the guidelines acknowledge that obesity—ABCD—is associated with a large number of comorbidities and complications.[59] There are limitations with using BMI as a cut off, such

as a dependency on patient ethnicity, but in general, they are a good starting point for discussions with patients. Talking about caveats.

**Figure 5.** Complications-centric model for the care of persons with overweight/obesity and ABCD

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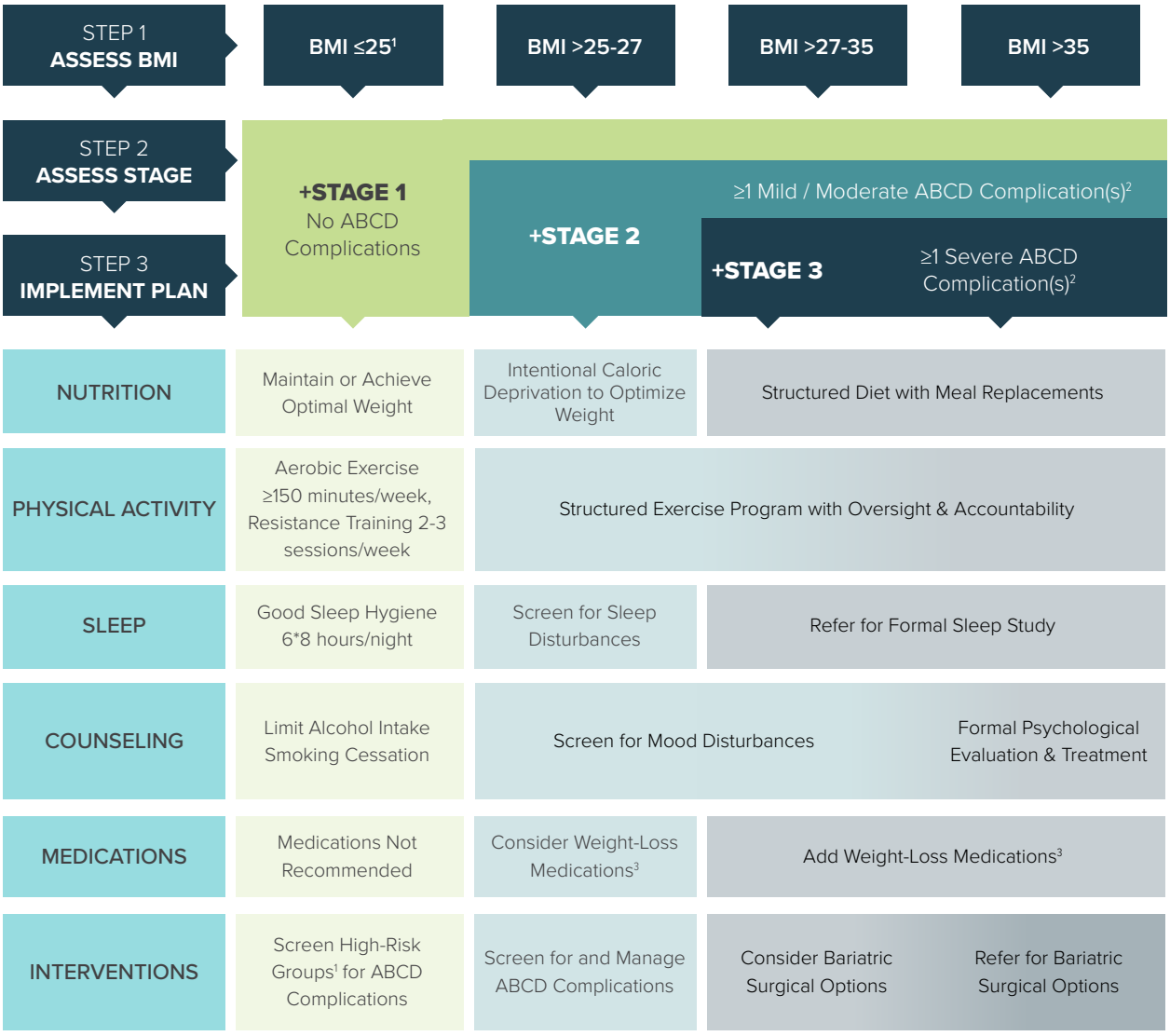


[1]BMI 23 to 25 kg/m$^2$ may be considered overweight for South Asian, Southeast Asian, and East Asian adults; [2]ABCD complications can include prediabetes, dyslipidemia, hypertension, NAFLD/NASH, ASCVD, CHF and HfpEF, CKD, OSA, OA, asthma/reactive airways disease, GERD, urinary incontinence, PCOS, hypogonadism, and reduced fertility.; [3]See PROFILES OF WEIGHT-LOSS MEDICATIONS table.

Practically, BMI thresholds for intervention can be reduced to between two to three points. Stage one, which is so-called normal weight patients, the guidelines are very simple. The principles work on nutrition, aerobic exercise, two to three sessions a week, optimal sleep hygiene, appropriate counseling to limit alcohol intake, and smoking cessation. Medications generally not required. If, however, they have some of these, the ABCD-related things, then specific interventions may be necessary.

In stage two, patients who are technically overweight require some management intensification such as intentional caloric restriction to optimize weight, a structured exercise program, screening for sleep disturbances, screening for mood problems, psychiatric or psychological problems, and a need to start considering weight loss medications. By the time patients get to stage three—severe ABCD complications –intensive attention and interventions are geared towards weight management, including bariatric surgery.

## PREDIABETES GUIDANCE

The prediabetic patient population represents a significant portion of the total population. It is important to look in their health records to confirm they do not have pre-diabetes or are at high risk for pre-diabetes but have not been evaluated. For patients with prediabetes, management starts with lifestyle interventions and cardiovascular risk reduction.[59] Cardiovascular risk reduction has similar targets to T2D. And if the patient is overweight or obese, then goal should be for at least 7%-10% weight loss. In this regard, the use of agents that are high efficacy, the GLP-I and GIP/GLP-1 RAs may prove useful. If the patient has persistent hyperglycemia, but do not have obesity or overweight, then the options are a little different. For these patients, consider metformin, pioglitazone, and acarbose.

## ASCVD GUIDANCE

The first order of business is complications, because this is what kills these patients. ASCVD complications are the greatest cost of mortality in this group of patients and cause significant morbidity. The first step is to measure their lipid levels. The major elements to look at include LDL, HDL, triglycerides, and apoB. Management begins with lifestyle interventions with medications added on. Statin therapy is recommended for all patients with diabetes unless there is a clear reason for not doing so.

The triglyceride goal is the same across all ASCVD risk levels. The APO-B less than 80 mg/dL. If the patient has extreme risk greater than 20%, it's even more intensive. And these are patients who have severe target organ disease already or who have already had another sclerotic event. Then you are looking at an LDL of less than 55 mg/dL, apo-B levels less than 70 mg/dL, and triglycerides less than 150 mg/dL. For patients with diabetes and hypertension, the use of ARBs or its inhibitors is recommended, barring a sound reason for not using them.

Once comorbidities have been addressed, glycemic control should be considered.[59] The guidelines recommend lifestyle interventions in each algorithm. The guidelines mention complication control independent of glycemic targets or whatever therapy they may be on. This is different from the way we used to approach this condition before, where recommendations focused on glucose first and recommended starting with metformin and building from there.

The guidelines walk through how to individualize glycemic targets and choosing therapy(ies). Therapy begins with metformin if appropriate and, if not a glycemic target at three months, titrate dose of medications to maximum and consider adding any of these other agents. If after a two-to-three-month period of intensive therapy the patient is not at goal, then you need to start thinking about basal insulin and other agents including prandial insulin.

## OLDER PATIENTS WITH DIABETES

The treatment of older patients with type 1 or type 2 diabetes tend to have had diabetes for a longer period of time. What that means is the complications of diabetes, prevalence of the complications of diabetes are significantly greater in this population, including cardiovascular complications.[60] In every major ASCVD index, whether it's CHF, coronary artery disease, angina, heart attacks, the prevalence in patients greater than 65 is significantly greater than those under 65.

The odds are high that geriatric patients are going to have one or more major diabetes complications. And so, consequently, that guideline suggests the following, that in patients who are older, it's worthwhile to categorize them as far as their health status. So-called good health patients who have no comorbidities and just one to two non-diabetes related chronic illnesses can have a fairly aggressive A1C target. However, in patients with group two, intermediate disease, more than three non-diabetes, chronic illnesses, already having some cognitive impairment, there is no reason to be chasing after the A1C in these patients. The guidelines are more liberal in these patients. And for group three, patients who are in poorer health, the guidelines are even more liberal. Choice of medications in this population is critical. Think carefully about insulin in these patients, especially if you're doing basal bolus.

**Figure 6.** Overall health and values in older patients

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| Overall Health Category | | GROUP 1<br>Good Health | GROUP 2<br>Intermediate | GROUP 3<br>Poor Health |
|---|---|---|---|---|
| Patient characteristics | | No comorbidities<br>OR<br>1-2 non-diabetes chronic illnesses AND 0-1 ADL impairments | ≥ non-diabetes chronic illnesses<br>AND/OR<br>Mild cognitive impairment or early dementia OR ≥2 IADL impairments | Any 1 of the following:<br>End-stage medical condition<br>Moder-severe dementia<br>≥2 ADL impairments<br>Long-term nursing facility residence |
| | | Reasonable glucose target ranges and HbA1c by group<br>Individualize goals through shared decision-making | | |
| Use of drugs that may cause hypoglycemia (eg. insulin, sulfonylurea, glinides) | No | Fasting: 90-130 mg/dL<br>Bedtime: 90-150 mg/dL<br><7.5% | Fasting: 90-150 mg/dL<br>Bedtime: 100-180 mg/dL<br><8.0% | Fasting: 90-180 mg/dL<br>Bedtime: 110-200 mg/dL<br><8.5% |
| | Yes | Fasting: 90-150 mg/dL<br>Bedtime: 90-180 mg/dL<br>≥7.0 – <7.5% | Fasting: 100-150 mg/dL<br>Bedtime: 150-180 mg/dL<br>≥7.5 – <8.0% | Fasting: 100-180 mg/dL<br>Bedtime: 150-250 mg/dL<br>≥8.0 – <8.5% |

## Summary

T2D is more than lowering A1C. Obesity is emerging as a treatable target that can delay progression from prediabetes to T2D and may be beneficial in treating T2D. However, even endocrinologists undervalue the importance of treating obesity in individuals with T2D, instead focusing on the traditional indicator of A1C. Past obesity medications were marginally effective and/or associated with substantial side effects. Recent recognition of the benefit of incretin therapies beyond A1C lowering has allowed these therapies to be used to treat obesity. The use of GLP-1 and GIP/GLP-1 receptor agonists is increasing and gradually overcoming therapeutic inertia to the treatment of obesity. Guidelines are evolving to reflect a complication-centric view of diabetes care that includes heart, kidney, and obesity care. Finally, clinicians who treat patients with diabetes and/or obesity should be aware of these updates and apply recent data to the care of their patients.

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