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Standard and Novel Treatment Options for Metabolic Syndrome and Diabetes Mellitus

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Abstract

Type II Diabetes and metabolic syndrome are two intertwined conditions that are critical to the healthcare landscape in the United States and abroad. Patients with either diabetes or metabolic syndrome can have a dramatically increased risk of developing cardiovascular disease. Numerous treatment options have existed for some time, which include non-pharmacologic and pharmacologic therapies. Additionally, within the last decade a multiple of novel treatment options have emerged for the management of hyperglycemia in particular. By targeting novel pathways beyond the secretion and supply of insulin, these new therapeutics provide a valuable adjunctive to the currently available therapies for diabetes and metabolic syndrome. Here we discuss the current guideline driven usage of standard therapies with some novel indications. In addition we discuss the novel therapies for the treatment of hyperglycemia, their mechanisms of action and appropriate therapeutic indications.

Keywords

Type II Diabetes; Cardiovascular Disease; Metabolic Syndrome; Diabetes Mellitus; Hyperglycemia

Introduction

Type II diabetes mellitus is a chronic medical condition that alters glucose metabolism and results in many detrimental effects if not properly treated. As with other endocrine diseases,

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Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

the adverse effects of diabetes can ravage many organ systems. Diabetic complications include an increased risk of cardiovascular disease(CVD), retinopathy, nephropathy, and neuropathy which arise due to micro and macrovascular disease [1]. While the onset of diabetes may be insidious, it is important to recognize and treat this disease in its early stages to avoid concurrent diagnosis of the complications associated with long standing disease [2]. For instance, the onset of diabetic retinopathy typically precedes the clinical diagnosis of diabetes by 4 to 7 years [3].

Metabolic syndrome is defined by a co-existence of numerous risk factors for Type II Diabetes and CVD [4]. The most commonly utilized criteria were set forth by the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) in 2005 [5]. This defines the syndrome as the presence at least of 3 of 5 risk factors, which are: impaired glucose metabolism, low HDL cholesterol, elevated triglycerides, abdominal obesity and elevated blood pressure [5]. Evaluated in 2001 by ATP III criteria, the prevalence of metabolic syndrome in the United States was 22% with a dramatic increase with advancing age [6]. Given that metabolic syndrome has been shown to be an important risk factor for the development of type II diabetes and CVD, it must be treated aggressively.

The approach to treating type II diabetes and metabolic syndrome includes the use of both non-pharmacologic and pharmacologic therapy [7]. Non-pharmacologic therapy includes a host of lifestyle changes and psychological interventions aimed at improving glycemic control and reducing cardiovascular risk without the use of medications [7]. Pharmacologic therapies in type II diabetes aim to modify the metabolic abnormalities associated with diabetes and improve glycemic control through numerous mechanisms. In the United States the most commonly prescribed medical therapy in diabetes continues to be Metformin which was first developed in the 1920's, showing that there is a market for novel therapies [8]. For metabolic syndrome, the mainstay of pharmacologic therapy is aimed at cardiovascular risk reduction through the use of lipid lowering agents and antihypertensive therapy [9].

Here we will review the established therapies for diabetes and metabolic syndrome, then expand our focus to the emerging and novel therapies for this very prevalent disease and important syndrome of risk factors. Glycemic control is difficult to achieve and maintain in many patients. However, it is critical; particularly in patients with known CVD as poor glycemic control is one of the most significant factors in the development and progression of CVD as well as microvascular complications [10].

Goals of Treatment

It has been well established that in Type I Diabetes a reduction in blood glucose concentrations to near normal levels is associated with a reduction in micro and macro vascular complications [11]. This tenet also holds true in type II particularly with regard to microvascular complications [12]. The hemoglobin A_{1c} is the standard measure for glycemic control, and each one percent drop in the A_{1c} has been shown to be related to reduced CVD outcomes. Randomized controlled clinical trials such as the Kumamoto Study, the United Kingdom Prospective Diabetes Study (UKPDS), and the Diabetes Control and Complications Trial (DCCT) have clearly demonstrated that intensive hypoglycemic therapy

resulted in decreased incidence of retinopathy, nephropathy and neuropathy with no threshold effect [13–15]. However, despite the established evidence that type II diabetes is a CVD risk factor, to this point, trials of intensive glycemic control have failed to establish a decrease in CVD outcomes in those with known CAD [16, 17]. Although those without CVD have shown a reduction in CVD outcomes in subgroup analysis [17]. At this time the American Diabetes Association (ADA) recommends that clinicians aim to achieve a level of normal of near normal glycemia with an A_{1c} of <7 percent [18]. Depending on patient factors such as hypoglycemic episodes, age, duration of diabetes, and comorbid conditions, this goal can change give recent trial evidence showing poor outcomes with intensive control in those with CVD [19].

Metabolic Syndrome is treated based on two major therapeutic goals set forth by the ATP III and reiterated by the American Heart Association (AHA), National Institutes of Health (NIH) and the Endocrine Society [20]. The first goal is to modify the patient's lifestyle to treat underlying causes such as obesity and inactivity through intense weight management and exercise [20]. Pharmacologic treatment of cardiovascular risk factors that persist despite lifestyle modifications is the second goal. These goals are aimed at preventing type II diabetes and CVD.

Lifestyle Modifications and Non-Pharmacologic Therapy

Weight Loss

The ADA recommends weight loss for all overweight or obese individuals at risk for diabetes. Even moderate weight loss (5% of body weight) can decrease fasting blood glucose, decrease A_{1c}, improve insulin action, and reduce need for oral hypoglycemics [21]. Furthermore, weight loss can improve other aspects of the metabolic syndrome including hypertension and hyperlipidemia. Among those with prediabetes, the Diabetes Prevention Program (DPP) among similar trials in Finland and China showed the powerful efficacy of lifestyle intervention in reducing the onset of new diabetes [22] In the Look AHEAD trial, a group a patients with type II diabetes who underwent bariatric surgery and had a sustained weight loss of >20 kg, virtually eliminated diabetes [23]. However, overweight or obese diabetes patients randomized to intensive lifestyle intervention did not decrease the rate of cardiovascular events [24].

Diet and Exercise

ADA recommendation is a diet low in carbohydrates and saturated/ trans-fats, and high in fiber. Exercise has a synergistic effect with diet in obtaining good glycemic control and leads to increased responsiveness to insulin, and may slow the progression of impaired glucose tolerance to diabetes [25]. Patients should have at least 150 minutes of moderate-intensity aerobic exercise per week [26].

Intensive Lifestyle Modification

Intensive lifestyle intervention programs involve weight loss, physical activity, and behavior modification. In the Look AHEAD trial, patients with type 2 diabetes were randomly assigned to intensive lifestyle intervention group or a standard diabetes education group

[23]. The intensive lifestyle intervention included calorie restriction, moderate intensity physical activity, and weekly sessions with registered dieticians, behavioral psychologists, and exercise specialists. After four years, those in the intensive lifestyle modification group had a higher mean weight loss, and were more likely to have complete or partial remission of diabetes [27]. However, there was no associating with improved outcomes in CVD as discussed previously. However, the overall trial was terminated early due to lack of efficacy in reducing CVD outcomes despite favorable benefits in reducing A1c and improving physical activity, although treatment group differences diminished with time [24]

Established Oral Hypoglycemic Therapy

The majority of patients are unable to maintain substantial weight loss or a regular exercise program, thereby limiting the role of lifestyle modifications and necessitating the use of pharmacologic therapy in the treatment of type II diabetes. Early initiation of pharmacologic therapy is associated with improved glycemic control and decreased chronic complications [28]. Here we review first line oral therapeutics. Table 1 outlines these oral hypoglycemic medications.

Metformin

Metformin is the initial pharmacologic therapy of choice for most diabetic. It reduces hepatic glucose production by stimulating AMP-activated protein kinases and lowers fasting glycemia. On average, monotherapy with metformin lowers HbA1c by 1.5% [29], and it can be combined with several other therapies including insulin. Generally well tolerated, it does not typically cause hypoglycemia. In contrast to many other glucose-lowering medications, weight stabilization and modest weight loss are typical. A rare (<1 case per 100,000 patients), but potentially fatal, side effect is lactic acidosis [30]. Thus, patients with renal dysfunction, decreased tissue perfusion from infection, liver disease or alcohol abuse should not use metformin. Metformin is taken with meals 2 to 3 times a day and increased slowly at intervals of 1–2 weeks. Other potential side effects of metformin include minor gastrointestinal side effects.

In the United Kingdom Prospective Diabetes Study (UKPDS), overweight patients with newly diagnosed type II diabetes treated with metformin rather than a sulfonylurea or insulin had decreased risk of diabetes related endpoint, all-cause mortality, and stroke [31]. Cardiovascular benefits of metformin demonstrated in UKPDS were supported by findings from a recent randomized trial comparing metformin and glipizide. After three years, mean A_{1c} levels were similar in both groups (7 and 7.1%), but body weight, waist circumference, and BMI were significantly lower in the metformin group. At 5 years, there were fewer major cardiovascular events (myocardial infarction (MI), stroke, revascularization, death) in the metformin group [32].

Sulfonylureas

Sulfonylureas are the oldest class of oral hypoglycemic medications and can be used as monotherapy, or in combination with other oral hypoglycemics or insulin. They enhance insulin release from beta cells by closing specific potassium channels. A reduction of A_{1c} by

1–2 percent and blood glucose by about 20 percent is typical [33]. Although sulfonylureas are rapidly effective, long term maintenance of glycemic targets is not as good as compared with metformin [34]. The structural characteristics of second generation sulfonylureas allow them to be given in lower doses than the rarely used first generation sulfonylureas.

The major side effect of sulfonylureas is hypoglycemia, which is more common in older patients. Glyburide and chlorpropamide are associated with a greater risk of hypoglycemia compared to other sulfonylureas [35]. Weight gain of approximately 2 kilograms is common. In the University Group Diabetes Program (UGDP), type II diabetics who received tolbutamide, a first generation sulfonylurea, were noted to have an increased cardiovascular mortality, which suggested an association of adverse CVD outcomes with sulfonylurea therapy [36]. However, this negative association has not been substantiated by the UKPDS or ADVANCE study [12, 17]. Among patients with CVD, there is also concern that sulfonylurea therapy may increase CVD risk and post MI mortality [37, 38]

Thiazolidinediones

Thiazolidinediones (TZDs) increase the sensitivity of muscle, fat, and the liver to endogenous and exogenous insulin. When used as monotherapy, TZDs decrease A_{1c} by 0.5–1.4 percent. Common side effects include fluid retention, peripheral edema, weight gain, and heart failure. Fluid retention is a result of PPAR-gamma stimulation of sodium reabsorption by sodium channels in the renal collecting tubule cells. There have been several randomized controlled trials investigating the cardiovascular effects of TZDs. Meta-analyses of rosiglitazone have shown adverse effects on cardiovascular outcomes. In a meta-analysis of 42 trials, rosiglitazone was associated with a significant increase in the risk of MI and an increase in risk of death from cardiovascular causes [39]. A recent secondary analysis of the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial suggested that using a TZD or metformin reduced the risk lower extremity revascularization, low ankle brachial index or amputation when compared to sulfonylurea, meglitinides or insulin. On the other hand, in the PROactive trial (Prospective pioglitazone clinical trial in macro vascular events), pioglitazone did not have a significant impact on the primary cardiovascular outcomes of composite all-cause mortality, nonfatal MI, stroke, revascularization after 3 years, and there was a modestly and statistically significant reduction in death, MI, and stroke [40].

TZDs are not recommended for patients with symptomatic heart failure. Per 2009 ACC/AHA guidelines, TZDs are contraindicated in patients with NYHA class III or IV heart failure [41]. The Food and Drug Administration (FDA) has issued a boxed warning for TZDs, and recommends that patients who take rosiglitazone or pioglitazone be observed for signs and symptoms of heart failure. Additionally, Aleglitazar, a new PPAR agonist, aimed to reduce macrovascular complications in patients with both type II diabetes and CVD. However phase III trials showed no benefit and several highly undesirable side effects [42]. In 2006, several other dual PPAR agonists such as tesaglitazar and muraglitazar failed to pass clinical trials due to safety concerns.

Meglitinides

Meglitinides stimulate insulin secretion and are hepatically metabolized. Repaglinide decreases A_{1c} by approximately 1.5 percent. The half-life of meglitinides is shorter than the sulfonylureas. Weight gain and hypoglycemia are common side effects, although hypoglycemia occurs less frequently than with sulfonylureas.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors slow the rate of polysaccharide digestion in the proximal small intestine and reduce post-prandial blood glucose levels. They lead to a modest reduction in A_{1c} by 0.5–0.8 percent, which is less effective than metformin or sulfonylureas [43]. Main side effects are flatulence and diarrhea. In a multi-center, randomized control trial, patients with impaired glucose tolerance who received acarbose had a 49 percent relative risk reduction in the development of cardiovascular events, and a 91 percent relative risk reduction in MI compared to controls [44]. This class should be considered in diabetics who have contraindications to metformin or sulfonylurea therapy.

Insulin Therapy

In a normal functioning pancreas insulin is secreted in a pulsatile fashion. There are un-stimulated small pulses and stimulated conditions, in response to oral intake, which are intended to maintain normal blood glucose levels. Typically, basal insulin secretion under normal physiologic conditions represents approximately 50 percent of daily insulin production. When prescribed as a therapy for type II diabetes, the patient should first have failed to maintain an adequate level of blood glucose control on at least one oral hypoglycemic [45]. Frequently, insulin will not be started until the patient is not well controlled on a combination of 2 to 3 non-insulin agents [46]. However, if the A_{1c} remains greater than 8.5 percent on one agent, insulin is the preferred second line treatment [45].

Insulin therapy is typically given in a manner that is designed at mimicking the physiologic secretion of insulin. This strategy has been referred to as both “intensive insulin therapy” and a “basal bolus” [47]. However in practice there are a host of methods used that are dependent on the prescribing clinician and the needs of the patient. In many diabetics a basal supplement in addition to non-insulin therapy is adequate to control the blood glucose. There are several formulations of insulin that vary in onset of action, duration and time to peak, among other differences (Table 2). These different formulations are typically used as either a basal supplement or a premeal bolus dose and are classified as human insulin preparations or insulin analogs. Insulin can also be given in a continuous subcutaneous infusion via an insulin pump. Advantages include flexibility with meal timing and improved glycemic control. Disadvantages include risk of infection, increased cost and increased risk of diabetic ketoacidosis.

Long Acting Insulin Preparations

Insulin Glargine—An insulin analog with one amino acid substitution and two additions, which delays subcutaneous absorption, and prolongs the duration of action [48]. Duration of

action is 24 hours and there is no appreciable peak, therefore this formulation is used frequently as a source of basal insulin with excellent efficacy [48].

Insulin Detemir—Detemir is an acylated insulin analog that allows for binding to albumin and therefore has a prolonged duration of action [49]. Duration is less than 24 hours and thus clinical trials have suggested that in order to achieve optimal control of blood glucose it needs to be dosed twice a day [49]. Additionally, detemir has a noticeable peak.

Insulin Degludec—Degludec is human insulin with a single amino acid deletion and a glutamyl link to a hexadecanedioic fatty acid which allows for the formation of multihexamers that slowly absorb [50]. Duration of action is more than 40 hours which in turn reduces the fluctuations in plasma concentration. An additional advantage over glargine and detemir is that degludec can be mixed with rapid acting insulins without an alteration in pharmacokinetics [50]. However this formulation is not available in the United States due to concern over an increase in cardiovascular risk, but is available in numerous other countries [51].

Intermediate Acting Insulin Preparations

NPH—A combination of insulin and protamine, which carries a positive charge, results in an intermediate duration of action that exceeds regular insulin, but is shorter than the long acting formulations [52]. Typically administered twice a day it can be mixed with shorter acting formulations and has an onset of action of 1 to 2 hours, a peak of 4 to 12 hours and a duration of 14–24 hours [52].

Neutral Protamine Lispro (NPL)—A longer duration version of the short acting insulin lispro, NPL is typically mixed in fixed doses with insulin lispro and has duration of 14–24 hours [53]. Typically is dosed twice daily, although given fixed concentrations can be difficult to achieve adequate glucose control.

Short Acting Insulin Preparations

Regular Insulin—With an onset of action in approximately 30 minutes and a peak effect of 2.5 to 5 hours, regular insulin has duration of 8 hours and is typically used as bolus insulin to cover oral intake in addition to longer acting insulin [53]. It can be delivered though a continuous insulin pump, subcutaneous injection and is being investigated for inhalation, which may be particularly useful in patients with subcutaneous insulin resistance syndrome [54].

Rapid Acting Insulin Preparations

Lispro—Lispro is short acting insulin with an onset of action of 15 to 30 minutes, peak effect of 30 minutes to 2.5 hours and duration of less than 5 hours [53]. Produced by reversing the amino acids on the C-terminal end of the beta chain in insulin, the reversal does not affect binding, but enable the rapid absorption and function [53].

Aspart—Identical to regular insulin with the exception of a single amino acid substitution, it has an onset of less than 20 minutes, a peak effect of 1 to 3 hours and duration of 3 to 5

hours [55]. The slight change in amino acid sequence allows for reduction in hexamer formation and thus rapid absorption and action [55].

Glulisine—Produced though two amino acid substitutions from regular insulin, glulisine is utilized both through subcutaneous injection and can be delivered intravenously in the critically ill. The onset of action is less than 30 minutes, with peak effect of 1.6 to 2.8 hours and duration of 3 to 4 hours [55].

Pharmacologic Therapy for Hyperlipidemia and Hypertension

Currently part of the mainstays for treatment of metabolic syndrome and type II diabetes is to reduce the risk of developing CVD is controlling the patient's lipids and blood pressure [7]. In patients with type II diabetes the recommendation is to achieve LDL cholesterol of less than 100 mg/dL, although some propose a more aggressive goal of 80 mg/dL [7]. This goal is typically achieved through the use of statin therapy. Although additional options are available for use and several novel therapeutics are being developed. In metabolic syndrome the evidence is not as well established as in type II diabetes, however a study by Deedwania, which was a post-hoc subgroup analysis, compared the use of high versus low dose atorvastatin in patients with metabolic syndrome and CVD, which showed a statistically significantly reduced rate of major adverse cardiovascular events at 5 years [56].

For hypertension, there is clear and well established data that treatment of patients with type II diabetes using angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) is beneficial [57]. Treatment with ACE inhibitors and ARBs reduces proteinuria, progression to diabetic nephropathy and may reduce insulin resistance. Goal blood pressure by major guidelines for type II diabetes suggests the goal blood pressure is 130/80 [18]. However, the ACCORD blood pressure trial included an aggressive therapy group (Systolic blood pressures < 120 mmHg) [58]. A meta-analysis of ACCORD and two other smaller trials (ABCD and HOT) suggested that intensive blood pressure lowering reduced the risk of stroke, but had no significant effect on mortality or MI [59]. In patients with metabolic syndrome, there is no clear indication for any particular antihypertensive. Therefore, current guidelines for treatment for uncomplicated hypertension should be followed which dictate a goal blood pressure under 140/90 mmHg [60].

Novel Therapies for Type II Diabetes and Impaired Glucose Metabolism

If patients fail to maintain their A_{1c} below the target goal on the standard therapies, then the initiation of an additional therapeutic can be indicated. Sub analysis of the UKPDS revealed that even patients who were initially well controlled on a single agent required a second agent in 50 percent of cases at three years and after nine years 75 percent of patients were taking multiple agents [61]. Generally it is the recommendation of the ADA is to add a standard agent such as those described above [18]. But in some cases this addition is either contraindicated, ineffective or there are additional therapeutic goals that would necessitate the addition of an alternate agent. Due to the need for alternate approaches and novel treatment options, several new classes of medications have been recently developed to meet this demand (Table 3).

Incretin Hormone Therapy

Insulin secretion from the pancreatic β-cells is a complex process regulated by a host of factors. One such regulatory mechanism is the function of Incretin hormones which help regulate insulin and glucagon secretion [62]. The major Incretins are Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) [62]. These glucose dependent hormones are secreted by the endocrine cells in the small intestine when glucose levels rise with ingestion of oral nutrition. Through activation of G protein coupled receptors in the pancreas, they stimulate the secretion of insulin. GLP-1 has several other effects which include stimulation of the secretion of glucagon, reduction in gastric emptying, decrease in appetite and increased sensation of satiety [19]. GIP and GLP-1 are rapidly degraded in vivo by a proteolytic enzyme Dipeptidyl Peptidase-4 (DPP-4) [62].

Patients who suffer from type II diabetes have altered incretin function due to a decrease in secretion and resistance. Therefore, this system was targeted for pharmaceutical development. The two classes of therapeutics developed were DPP-4 resistant GLP-1 Receptor Agonists and DPP-4 inhibitors. These therapies are generally not considered as first line therapy, but as an adjunctive measure in those whom cannot achieve adequate control of their blood glucose with standard agents [18]. To this point no major studies have examined the effects of incretin based treatments on CVD outcomes. Additionally, due to limited clinical data, long term effects are not yet known and as recently as March of 2013 the FDA is investigating unconfirmed reports of pancreatic toxicity.

Glucagon-Like Peptide-1 Receptor Agonists—Exenatide is a GLP-1 analog delivered by subcutaneous injection that was approved by the FDA in 2005 [62]. There are two formulations; the standard dosing regimen for the shorter acting formulation is one injection 60 minutes prior to the first and last meals of the day. The extended release formulation requires a once weekly dose. It is an analog of the native peptide exendin-4 which is similar to GLP-1 and binds avidly to the GLP-1 receptors in the pancreas. An adjunctive benefit of the medication is that it typically produces weight loss. Common side effects include gastrointestinal upset, nausea and diarrhea. It typically is expected to a patients hemoglobin A_{1c} by roughly 0.5 to 1 percent [62].

Liraglutide is also a GLP-1 analog delivered by subcutaneous injection that was FDA approved in 2010. Dosing is once daily and due to that regimen is felt to be more efficacious with fewer side effects than the twice a day formulation of Exenadtide [63]. Slower degradation is due to non-covalent binding of Liraglutide to serum albumin and the compounds acetylation of the native GLP-1 structure [63]. Currently there is an ongoing clinical trial (NN9924) of an oral formulation.

Dipeptidyl Peptidase-4 Inhibitors—In the United States there are four DPP-4 inhibitors available for clinical use. All taken by mouth, they are Sitagliptin, Saxagliptin, Linagliptin and Alogliptin. DPP-4 inhibtors are commonly utilized as a second or third agent, but can be utilized as a monotherapy in those with contraindications or intolerance to Metformin, Sulfonylureas or TZDs [18]. Sitagliptin was the first DPP-4 inhibitor approved by the FDA in 2006 and like all others is dosed in a once daily fashion [64]. These small molecules are

rapidly absorbed and result in a 2 to 3 fold increase in the concentration of GLP-1 and GIP in plasma. Studies typically result in a 0.6 to 0.9 percent reduction in A_{1c} with neutral effects on weight [64]. There is also felt to be some enhancement of pancreatic β-cell function. Early in the course of type II diabetes when a patient first requires a second agent in addition to Metformin, the DPP-4 inhibitors can be very effective [64]. Some of the DPP-4 inhibitors (Sitagliptin and Saxafliptin) have FDA approval in a combination pill with Metformin.

DPP-4 inhibitors and GLP-1 analogs are unlikely to cause hypoglycemia when used as a monotherapy. While it is unclear if there is a quantifiable clinical benefit the incretin based mimetics have also been shown to modify cardiac risk factors such as blood pressure, triglycerides, low density lipoprotein (LDL) cholesterol and weight [65]. Trials are also underway to determine if these compounds have an effect on CVD risk [65].

Amylin Agonists

Amylin is a neuroendocrine hormone which slows gastric emptying, increases satiety, and inhibits postprandial glucagon secretion [66]. It is secreted with insulin in response to oral nutrition, but its effectiveness and secretion is reduced in type II diabetes [19]. Approved in 2005 by the FDA, Pramlintide is a synthetic analogue of human amylin and is delivered subcutaneously before meals. Currently FDA approval is for use as an adjunctive therapy to insulin, unfortunately it cannot be mixed with insulin for injection [67]. Reductions in A_{1c} from 0.5 to 0.7 percent are expected, however this is at the expense of risks for hypoglycemic episodes and a relatively high rate of gastrointestinal side effects [67, 68]. Weight loss over six months is expected of 1 to 1.5 kilograms [67, 68]. Due to its delay in gastric emptying Pramlintide will slow absorption of oral medications and should not be given in patients with gastroparesis [68]. Pramlintide, as an adjunct to basal insulin, was associated with improvements in several cardiovascular risk markers in one study [69].

Sodium-Glucose Co-Transporter 2 Inhibitors

The sodium-glucose co-transporter 2 (SGLT2) is a protein located in the proximal tubule of the nephron and mediates reabsorption of around 90 percent of the filtered glucose load [70]. By inhibiting the transport protein, renal excretion of glucose is increased and thus blood glucose levels are decreased. Blood glucose reductions are independent of insulin, but are dependent on filtered glucose loads and osmotic diuresis. This class of medications is less effective in those with chronic kidney disease [70]. The FDA only first approved SGLT2 inhibitors in March of 2013 with the compound Canagliflozin [71, 72]. SGLT2 inhibitors are taken orally once a day before the first meal of the day. Dapagliflozin is another SGLT2 inhibitor that is only available outside of the United States. This class has been studied as a monotherapy and in conjunction with several oral hypoglycemic and insulin [71, 72]. Modest reductions in A_{1c} are seen with SGLT2 inhibitors, with an average of 0.5 to 0.7 percent, similar oral DPP-4 inhibitors [71, 72]. Although a recent head to head comparison showed Canagliflozin was superior to Sitagliptin when combined with metformin and sulfonylurea [73]. Reductions in blood pressure and weight were also seen across nearly all trials involving SGLT2 inhibitors, potentially strengthening indications in metabolic syndrome [71]. Side effects include an increase in genitourinary tract infections.

Canagliflozin cannot be taken if the patients glomerular filtration rate (GFR) is less than 45 mL/min, or if the patient has significant hepatic impairment [71].

Conclusions

As the population ages and the incidence of type II diabetes and metabolic syndrome continues to increase, it is critical that clinicians understand the availability and mechanism of treatment options. Over the past decade several novel treatment options have become available for the hyperglycemia associated with metabolic syndrome and type II diabetes. New therapeutics target various hormone pathways and glucose transporters. These medications can be used in concert with long standing standard therapies, or as first line therapy in some cases. New data may emerge suggesting even further benefit from these agents with time. Additionally it is important to understand the treatment guidelines for both metabolic syndrome and type II diabetes. We have given an overview of the standard treatments and thoroughly reviewed the novel therapeutics available for use. This information should be used to make appropriate choices for individualized patient care.

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• Of importance

•• Of outstanding importance

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Table 1

Oral Hypoglycemics for Type II Diabetes and Impaired Glucose Metabolism

Therapeutic Class	Mechanism of Action	Benefit	Risks
Biguanides	Decreases hepatic glucose production, decreases intestinal glucose absorption, improves insulin sensitivity	Weight stabilization and potential weight loss	Gastrointestinal side effects, lactic acidosis (rare)
Sulfonylureas	Stimulates insulin secretion by inhibition of ATP-dependent potassium channels in the pancreatic beta cell	Rapidly effective	Weight gain, hypoglycemia
Thiazolidinediones	Increases insulin sensitivity through the binding and activation of peroxisome proliferator-activated receptors (PPAR)	Improvement in lipid profile	Heart failure, fluid retention, weight gain, potential increase in MI (rosiglitazone)
Meglitinides	Stimulates insulin secretion by inhibition of ATP-dependent potassium channels in pancreatic beta cells	Rapidly effective	Hypoglycemia, weight gain
Alpha-glucosidase inhibitors	Slows absorption of glucose and reduces postprandial serum glucose levels by inhibition of upper GI enzymes	Little effect on weight	Gastrointestinal side effects

Table 2

Insulin Formulations

Preparation	Available Formulations	Onset of Action	Peak Action (Hours)	Duration of Action (Hours)
Long Acting	Glargine	3–4 hours	None	≥24
	Detemir	3–4 hours	3–9	6–23
	Degludec	30–90 minutes	None	≥40
Intermediate Acting	NPH	1–2 hours	4–12	14–24
	NPL	15–30 minutes	0.5–13.5	14–24
Short Acting	Regular Insulin	30 minutes	2.5–5	8
Rapid Acting	Lispro	15–30 minutes	0.5–2.5	≤5
	Aspart	≤20 minutes	1–3	3–5
	Glulisine	≤30 minutes	1.6–2.8	3–4

Table 3

Novel Therapies for Type II Diabetes and Impaired Glucose Metabolism

Therapeutic Class	Available Formulations	Route of Administration	Hemoglobin A_{1c} Reduction	Contraindications
Incretin Based Therapies				
GLP-1 Receptor Agonists	Exenatide, Liraglutide	Subcutaneous Injection	0.5 to 1%	GFR<30 mL/min, Family history of Medullary Thyroid Carcinoma
DPP-4 Inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin	Oral	0.6 to 0.9%	Episodes of Diabetic Ketoacidosis
Amylin Receptor Agonists	Pramlintide	Subcutaneous Injection	0.5 to 0.7%	Frequent Hypoglycemic Episodes, Gastroparesis
SGLT-2 Inhibitors	Canagliflozin	Oral	0.5 to 0.7%	GFR<45 mL/min, Hepatic Impairment