

# Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options

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**Abstract:** Diabetes is a complex and progressive disease that has a major societal and economic impact. The most common form of diabetes, type 2 diabetes mellitus (T2DM), is a multifactorial disease, the pathophysiology of which involves not only the pancreas but also the liver, skeletal muscle, adipose tissue, gastrointestinal tract, brain, and kidney. Novel therapies with mechanisms of action that are different from most existing drugs are emerging. One such class consists of compounds that inhibit renal sodium-glucose cotransporter 2, which is responsible for the bulk of glucose reabsorption by the kidneys. This new class of compounds improves glycemic control independently of insulin and promotes weight reduction, providing an additional tool to treat patients with T2DM. This review discusses the underlying pathophysiology of T2DM, clinical guidelines, and available and emerging treatment options, with particular emphasis on sodium-glucose cotransporter 2 inhibitors.

**Keywords:** diabetes, hyperglycemia, oral antidiabetic therapies, pharmacotherapy, sodium-glucose cotransporter 2

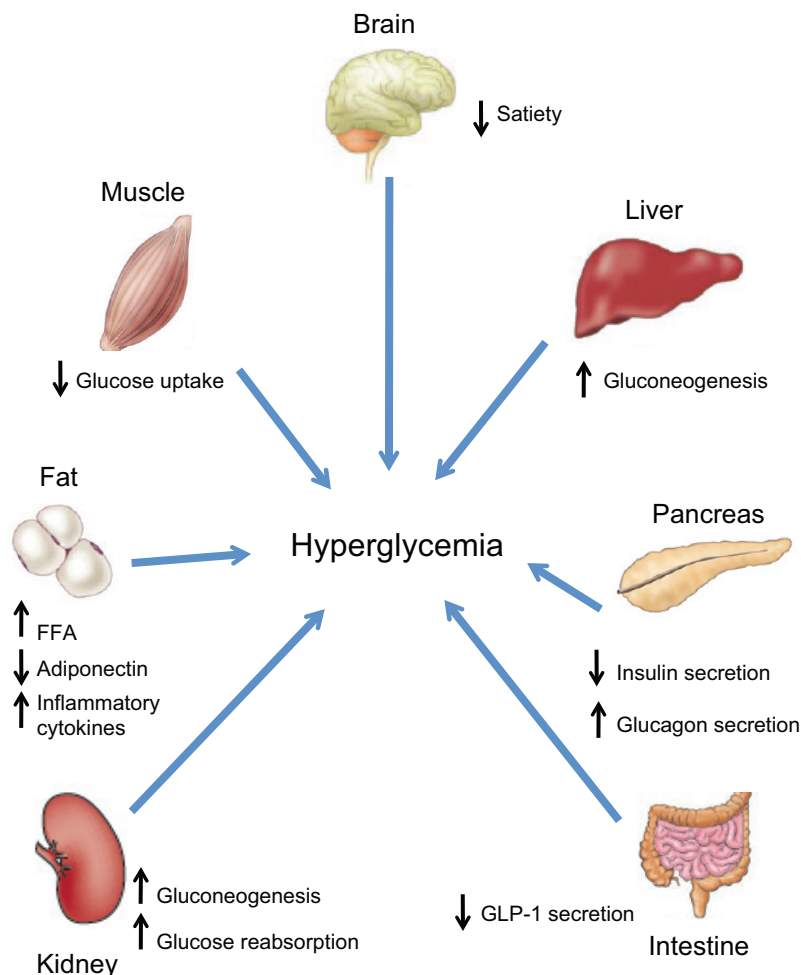
## Introduction

Diabetes is a complex and potentially debilitating disease that affects an estimated 8.3% of the adult population or 382 million people worldwide.<sup>1</sup> The region with the highest number of adults with diabetes, ie, 138 million, is the Western Pacific, which includes the People's Republic of China.<sup>1</sup> It is estimated that 29.1 million people in the USA (9.3% of the population) have diabetes.<sup>2</sup> If current trends continue, it is estimated that 592 million people worldwide will have diabetes by 2035.<sup>1</sup>

Diabetes care has a major economic impact in both developed and developing countries. Estimated global health care costs to treat and prevent diabetes were at least \$548 billion in 2011.<sup>1</sup> In the USA, the total cost of diabetes was estimated to be \$245 billion in 2012<sup>2</sup> and may exceed \$500 billion by 2025.<sup>3</sup>

Type 2 diabetes mellitus (T2DM) accounts for 90%–95% of new cases of diabetes.<sup>2</sup> T2DM pathophysiology involves at least seven organs and tissues, including the pancreas, liver, skeletal muscle, adipose tissue, brain, gastrointestinal tract, and kidney (Figure 1).<sup>4</sup> Reduced sensitivity to insulin (ie, impaired insulin-mediated glucose disposal or insulin resistance) in liver, muscle, and adipose tissue, and a progressive decline in pancreatic  $\beta$ -cell function leading to impaired insulin secretion, eventually result in hyperglycemia, the hallmark feature of T2DM. The purpose of this review is to discuss the underlying pathophysiology of T2DM, clinical treatment guidelines, and available and emerging treatment options, with emphasis on the newest class of antihyperglycemic drugs, the sodium-glucose cotransporter 2 (SGLT2) inhibitors.

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**Figure 1** Multiorgan and tissue pathophysiology of type 2 diabetes.

**Notes:** Adapted with permission from DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773–795.<sup>4</sup>

**Abbreviations:** FFA, free fatty acids; GLP-1, glucagon-like peptide-1.

## Pathophysiology Pancreas

Impairment of insulin action and of  $\beta$ -cell function occurs very early in the development of T2DM.<sup>5</sup> Insulin resistance can be detected in individuals with normal glucose tolerance who are at higher risk for development of T2DM 10–20 years before the disease is diagnosed.<sup>6</sup> Further, individuals who are transitioning from impaired glucose tolerance to T2DM may have already lost up to 80% of their  $\beta$ -cell function.<sup>4</sup> Mechanisms thought to play a role in the decline of  $\beta$ -cell function include the following:

### Genetics

The clustering of T2DM in families has long been recognized.<sup>7</sup> A number of genes associated with insulin and  $\beta$ -cell dysfunction have been identified in patients with T2DM, including genetic variants associated with pancreatic

development and insulin storage and secretion.<sup>8</sup> With insulin resistance comes an increased need for biosynthesis and release of insulin. It has been proposed that a genetic polymorphism in patients predisposed to T2DM results in failure of the  $\beta$  cell to adapt to the increased demand for insulin.<sup>9</sup>

### Age

Numerous studies have demonstrated an age-related decline in  $\beta$ -cell function and insulin secretion.<sup>10</sup> This is consistent with the increased prevalence of T2DM with aging.<sup>2</sup>

### Diet and exercise

Obesity and physical inactivity are major factors in the increased prevalence of T2DM worldwide<sup>11</sup> and are associated with insulin resistance.<sup>4</sup> Diets high in rapidly absorbable carbohydrates result in elevated insulin and blood glucose levels,<sup>11</sup> and the deposition of fat in liver and muscle increases

insulin resistance in these tissues.<sup>4</sup> These factors increase the demand for insulin, and in the long term may lead to progressive  $\beta$ -cell failure.<sup>4,11</sup>

### Glucotoxicity

Chronic exposure to elevated glucose concentrations impairs  $\beta$ -cell function and insulin secretion. The mechanisms involved in glucotoxicity remain to be elucidated but likely involve impairment of insulin gene expression, chronic oxidative stress, and apoptosis.<sup>12</sup>

### Lipotoxicity

Elevated plasma concentrations of free fatty acids (FFAs) impair insulin secretion in patients at risk for development of T2DM.<sup>13,14</sup> Elevated FFAs in  $\beta$ -cells lead to increased oxidative stress and apoptosis.<sup>15</sup>

### Liver

The liver is the main organ responsible for glucose production.<sup>16</sup> Hepatic glucose production and release into the circulation comes from both gluconeogenesis and glycogenolysis.<sup>16,17</sup> In patients with T2DM, the liver overproduces glucose because it becomes resistant to the suppressive effects of insulin.<sup>4</sup> Other factors, such as lack of suppression of postprandial glucagon secretion from pancreatic  $\alpha$  cells in patients with T2DM,<sup>18</sup> increased circulating glucagon, and increased sensitivity of the liver to glucagon, also contribute to increased hepatic glucose production.<sup>4</sup>

### Muscle

Insulin-stimulated transport of glucose into skeletal muscle is the primary mechanism for the disposal of an exogenous glucose load.<sup>19</sup> The major transporter involved in the uptake of glucose into skeletal muscle, glucose transporter 4 (GLUT4),<sup>19</sup> is also expressed in adipocytes and cardiac muscle and is responsible for insulin-stimulated glucose uptake into these tissues.<sup>20</sup> Insulin and exercise acutely stimulate the translocation of GLUT4 to the membrane of muscle cells, resulting in increased glucose uptake.<sup>19,20</sup> In patients with T2DM, skeletal muscle is resistant to the actions of insulin because of defects in insulin signaling and often a low level of physical activity.<sup>21</sup> This leads to a decrease in glucose uptake that contributes to the development of hyperglycemia.

### Adipose tissue

In patients with T2DM, adipocytes are resistant to the antilipolytic effect of insulin, resulting in elevation of circulating FFAs. Chronic increases in FFAs stimulate

gluconeogenesis, induce hepatic and muscle insulin resistance, and impair insulin secretion.<sup>22</sup> These lipid-induced changes in T2DM are part of a constellation of changes induced by excess FFAs, termed lipotoxicity.<sup>15</sup> Dysfunctional adipose tissue produces excessive amounts of inflammatory and atherogenic cytokines that can induce insulin resistance and concurrently fails to adequately secrete insulin-sensitizing adipocytokines.<sup>22</sup>

Much interest has recently been focused on “brown fat”, a very metabolically active adipose tissue previously thought to be present only in small mammals and newborn humans, where it functions in cold-induced or diet-induced heat production.<sup>23</sup> However, recent studies have shown that brown fat is also present in human adults.<sup>24–27</sup> In contrast with white adipose tissue, which stores excess energy as triglycerides,<sup>23</sup> brown adipose tissue uses small intracellular triglyceride vacuoles as a main energy source to produce heat.<sup>28</sup> The mass of brown fat has been shown to be directly related to resting metabolic rate<sup>26</sup> and inversely correlated with age, total body fat, and body mass index.<sup>24–26</sup> In addition, exercise has been shown to induce the “browning” of white adipose tissue.<sup>29</sup> These findings suggest that brown fat may play an important role in energy metabolism and in body weight control. However, the role of brown fat in the pathogenesis of T2DM is unclear.

### Brain

Insulin can cross the blood-brain barrier and, by modulating the expression of various neuropeptides involved in food intake, suppress appetite.<sup>30</sup> In patients with T2DM, the brain may become insulin resistant, such that the inhibitory effect of insulin on appetite is lost.<sup>30</sup> In fact, central insulin resistance may develop in individuals at risk for T2DM who are otherwise healthy.<sup>31</sup>

Amylin, a peptide synthesized and cosecreted with insulin from  $\beta$  cells, decreases food intake<sup>32</sup> by sensitizing the area postrema and nucleus of the solitary tract to other metabolic signals that reduce food intake, such as cholecystokinin and glucose.<sup>33</sup> Amylin also slows gastric emptying, and reduces postprandial glucagon release.<sup>32</sup> In patients with T2DM, as  $\beta$ -cell function progressively declines, amylin secretion is reduced and its satiety-producing effects wane.<sup>32</sup>

Leptin and ghrelin are two other hormones that act centrally to control food intake and body weight homeostasis. Leptin is mainly produced and secreted by adipocytes,<sup>34</sup> and its blood concentration is proportional to the percentage of body fat.<sup>35</sup> A major effect of leptin is to decrease food intake and body weight by acting on areas in the hypothalamus

involved in feeding behavior and energy balance.<sup>36</sup> Many individuals with T2DM are obese, have high circulating levels of leptin, and are resistant to exogenous leptin.<sup>34</sup> However, a subset of obese individuals has low levels of leptin and in these individuals exogenous leptin improves obesity.<sup>37</sup> Although exogenous leptin prevents insulin resistance in animal models of diabetes,<sup>38</sup> treatment of obese patients with T2DM did not improve insulin sensitivity.<sup>39</sup>

Ghrelin is secreted mainly by the stomach during fasting or caloric restriction and acts in the central nervous system to promote food intake.<sup>40</sup> Ghrelin and its receptor are also present in pancreatic islet cells.<sup>41,42</sup> In healthy humans, exogenous ghrelin reduces insulin secretion<sup>43,44</sup> and causes hyperglycemia.<sup>43,45</sup> In a population-based study, low plasma ghrelin concentrations were associated with increased fasting insulin concentrations, insulin resistance, and an increased prevalence of T2DM.<sup>46</sup>

## Gastrointestinal tract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones released by the gastrointestinal tract (incretins) in response to nutrient ingestion.<sup>47</sup> GLP-1 and GIP act on  $\beta$  cells to stimulate the release of insulin and are responsible for up to 60% of insulin secretion following a meal.<sup>48</sup> GLP-1 also promotes satiety, slows gastric emptying, and inhibits glucagon secretion, thus reducing hepatic glucose production.<sup>49</sup> Patients with T2DM have impaired secretion of GLP-1 and reduced responsiveness to GIP.<sup>48</sup> This results in increased gastrointestinal motility, decreased glucose-dependent insulin secretion, increased glucagon secretion, and increased liver glucose release, all of which adversely affect glycemic control.

## Kidney

Under normal conditions, more than 99% of glucose filtered by the kidneys is reabsorbed in the proximal tubule.<sup>50</sup> The bulk of glucose is reabsorbed by the SGLT2, in concert with a facilitative glucose transporter, GLUT2.<sup>50</sup> Once plasma glucose concentrations exceed the renal threshold for reabsorption (approximately 180 mg/dL in healthy individuals), glucose starts to appear in the urine.<sup>51</sup> A recent study demonstrated that the capacity of the kidney to reabsorb glucose is increased in patients with T2DM compared with matched healthy individuals.<sup>52</sup> Therefore, in patients with T2DM, the kidneys reabsorb glucose in excess and return it to the circulation, potentially worsening hyperglycemia.

The liver and kidneys are the only organs that possess the requisite enzymes for gluconeogenesis and that subsequently

release newly formed glucose into the circulation.<sup>16</sup> In the postabsorptive (fasting) state in healthy humans, renal gluconeogenesis accounts for approximately 20% of total glucose released into the circulation, with the liver contributing the remainder.<sup>16,53</sup> It has been suggested that renal glucose synthesis is increased in patients with T2DM relative to healthy individuals.<sup>54</sup> Therefore, in patients with T2DM, the kidneys may further exacerbate hyperglycemia by continued glucose reabsorption and increased production of glucose.

## Treatment goals

T2DM is a major risk factor for the development of cardiovascular disease,<sup>55</sup> as well as microvascular complications, including chronic kidney disease,<sup>56</sup> end-stage renal disease requiring dialysis or transplantation,<sup>57</sup> and blindness.<sup>2</sup> Hyperglycemia is the key determinant of microvascular complications. Randomized controlled trials have shown that intensive glycemic control can reduce the risk of microvascular complications in patients with T2DM.<sup>58–60</sup> Therefore, the major treatment goal for T2DM is to reduce hyperglycemia and to manage comorbidities, especially those associated with cardiovascular disease (hypertension and dyslipidemia). Lifestyle changes (diet and exercise) and intensive pharmacotherapy of hyperglycemia and of multiple risk factors substantially reduce the rates of death, cardiovascular events, and progression to end-stage renal disease and retinopathy in patients with T2DM.<sup>61</sup>

Hyperglycemia should be monitored over the long term by measurement of glycated hemoglobin ( $A_{1C}$ ) at least twice a year in all patients with diabetes and at least four times yearly in patients who are not at target.<sup>62</sup> Management of hyperglycemia should be individualized based on life expectancy, duration of T2DM, presence of comorbidities or vascular complications, potential for hypoglycemia or other adverse events, and patients' attitudes and access to support systems.<sup>62,63</sup> The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinologists (AACE) recommend general  $A_{1C}$  target levels  $<7.0\%$  and  $\leq 6.5\%$ , respectively, for most patients.<sup>62,63</sup> Strict control of blood pressure (BP) and lipids is also recommended.

## Pharmacotherapy

Lifestyle changes that include a healthy diet, weight loss, increased physical activity, self-monitoring of blood glucose, and diabetes self-management education have broad benefits in controlling hyperglycemia and cardiovascular risk factors in patients with T2DM.<sup>64</sup> Moreover, early intervention

with intensive lifestyle changes can prevent or delay the development of T2DM in susceptible individuals.<sup>65</sup> However, lifestyle changes may not be adequate to control hyperglycemia in the long term, and most patients will require pharmacotherapy to achieve and maintain glycemic control.<sup>64</sup>

Patients with T2DM usually require multiple medications to adequately treat their diabetes and associated comorbidities. There is currently no single agent available that affects all seven organs and tissues involved in the pathogenesis of T2DM; most drugs target up to four of the physiologic abnormalities.<sup>64</sup> The major classes of drugs, mechanisms of action, and major contraindications are shown in Table 1. The ADA/EASD treatment recommendations (Figure 2) stress the importance of individualization of treatment and treatment intensification with combination therapy if  $A_{1C}$  goals are not

attained. The ADA/EASD recommendations are based on the glucose-lowering effect, actions that may reduce long-term complications, tolerability, safety, ease of use, and expense of glucose-lowering medications.<sup>62</sup> The AACE algorithm for the treatment of T2DM also emphasizes the importance of individualized glycemic goals and treatment regimens, and stratifies treatment options based on initial  $A_{1C}$ .<sup>63</sup>

Despite the availability of several glucose-lowering drug classes, a recent survey of patients with diagnosed diabetes from 1999 to 2006 found that only 57% achieved an  $A_{1C}$  <7%, and only 12% achieved the recommended  $A_{1C}$ , BP, and low-density lipoprotein cholesterol goals.<sup>66</sup> The reasons for failure to achieve recommended treatment goals may include lack of treatment initiation and intensification, patient nonadherence,<sup>67</sup> and progressive decline in  $\beta$ -cell function,

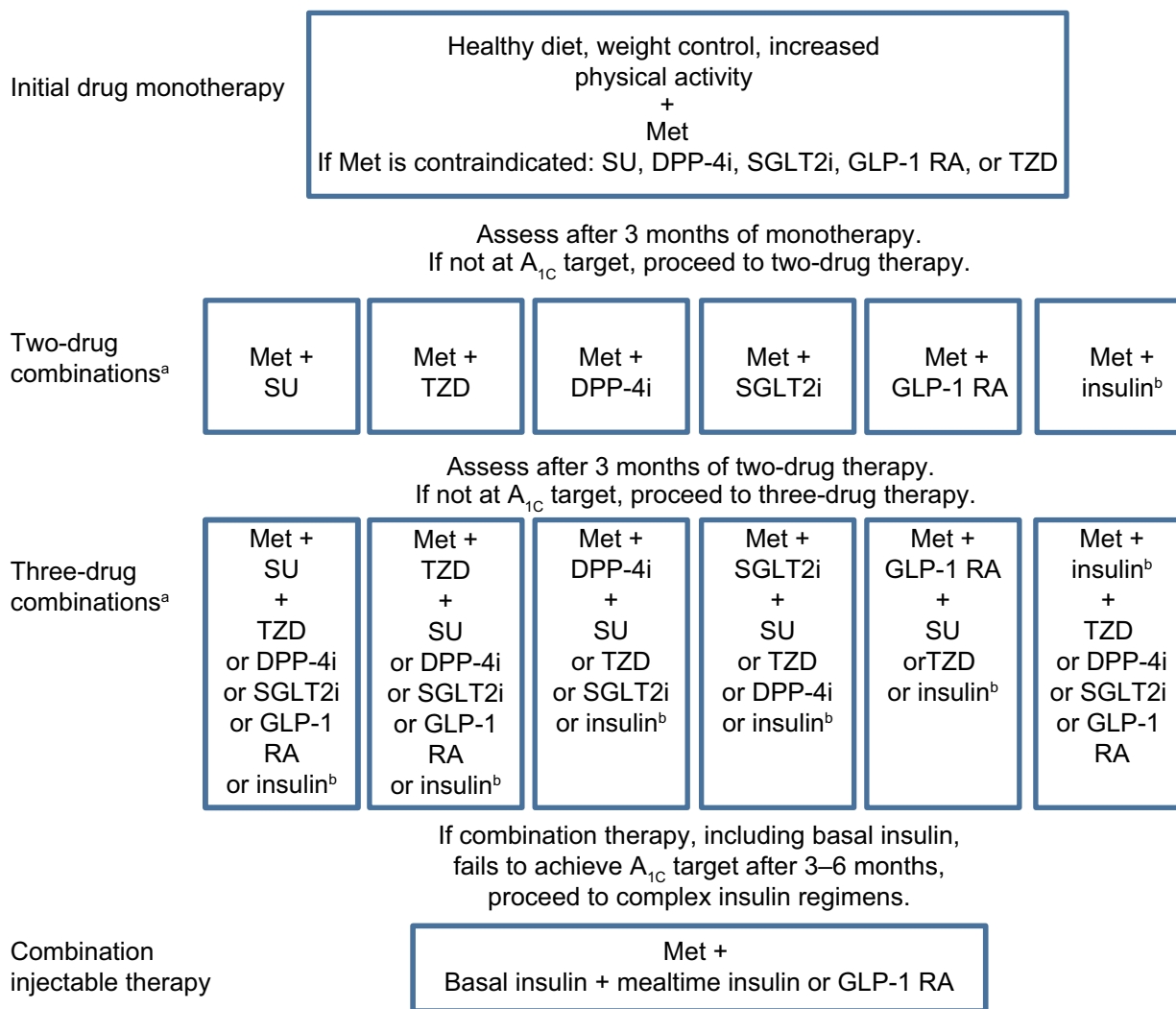
**Table 1** Drugs available for type 2 diabetes mellitus

Class	Mechanism of action	Glucose target	Major precautions, contraindications, adverse effects
<b>Oral agents</b>			
Biguanide (metformin)	Decreases hepatic glucose production; hepatic insulin sensitizer; decreases intestinal glucose absorption	Fasting	Gastrointestinal symptoms, lactic acidosis, contraindicated in renal insufficiency
Sulfonylurea (glyburide, glipizide, glimepiride)	Increases insulin secretion	Fasting and postprandial	Weight gain, hypoglycemia
$\alpha$ -glucosidase inhibitor (acarbose, miglitol)	Delays carbohydrate absorption	Postprandial	Gastrointestinal symptoms
Thiazolidinedione (pioglitazone, rosiglitazone)	Insulin sensitizer	Fasting and postprandial	Edema, weight gain, bone fractures, may cause or exacerbate heart failure, contraindicated in heart failure. Rosiglitazone has been withdrawn from the EU owing to potential increased risk of CV events. Pioglitazone may be associated with an increased risk of bladder cancer.
Meglitinide (nateglinide, repaglinide)	Increases insulin secretion	Postprandial	Weight gain, hypoglycemia
DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Increases GLP-1 and GIP levels	Postprandial	Urticaria/angioedema
Dopamine agonist (bromocriptine)	Modulates central neurotransmitters, resulting in improved glycemic control and glucose tolerance	Postprandial	Orthostatic hypotension, syncope, nausea
Bile acid sequestrant (colesevelam)	Lowers plasma glucose and LDL cholesterol	Postprandial	Constipation
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	Increase renal glucose excretion	Fasting and postprandial	Genital and urinary tract infections. Contraindicated in moderate to severe renal impairment
<b>Injectable agents</b>			
GLP-1 receptor agonist (exenatide, exenatide long-acting release, liraglutide)	Increases glucose-dependent insulin secretion, decreases glucagon secretion, slows gastric emptying	Postprandial, some fasting	Gastrointestinal symptoms
Amylin analog (pramlintide)	Delays gastric emptying, decreases glucagon secretion	Postprandial, some fasting	Hypoglycemia, gastrointestinal symptoms
Insulin (various analogs)	Stimulate glucose uptake	Basal, fasting bolus, postprandial	Weight gain, hypoglycemia

**Notes:** Data from.<sup>123–128</sup>

**Abbreviations:** CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; EU, European Union; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; SGLT2, sodium-glucose co-transporter 2.





**Figure 2** General recommendations for the treatment of type 2 diabetes from the American Diabetes Association/European Association for the Study of Diabetes.

**Notes:** <sup>a</sup>Order of drugs does not denote any specific preference; <sup>b</sup>usually basal insulin. Copyright © 2009. American Diabetes Association. Adapted with permission from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.<sup>124</sup>

**Abbreviations:** DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist;  $A_{1c}$ , glycated hemoglobin; Met, metformin; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

rendering therapies dependent on insulin secretion or action less effective over time.<sup>5</sup> Accordingly, new pharmacologic therapies with mechanisms of action that are independent of insulin secretion or action and with acceptable safety profiles and a low risk of hypoglycemia and weight gain may enhance the ability of patients to achieve and maintain glycemic control.

## New and emerging therapies

### SGLT2 inhibitors

As discussed above, the kidney plays an important role in glucose homeostasis. Inhibition of the major transporter involved in glucose reabsorption by the kidney, SGLT2,<sup>68</sup> is an attractive, insulin-independent mechanism for increasing urinary glucose excretion in the setting of hyperglycemia.<sup>69</sup>

Because the actions of SGLT2 inhibitors are independent of insulin, there is less risk of major hypoglycemic events<sup>70</sup> compared with agents dependent on insulin action, and there is also the potential for effectiveness in advanced disease. Moreover, increased excretion of glucose and associated calories by SGLT2 inhibitors decreases body weight.<sup>71</sup> Finally, there is a potential for combination therapy with other classes of agents with complementary mechanisms of action to optimize treatment.<sup>72</sup> However, because the mechanism of action of SGLT2 inhibitors depends on the filtration of glucose by the kidney, as the glomerular filtration rate (GFR) declines, the amount of glucose filtered is reduced, which decreases glucosuria and the efficacy of these drugs.<sup>73</sup> A number of selective SGLT2 inhibitors are in various stages of clinical development for the treatment of T2DM.<sup>74</sup>

## Dapagliflozin

Dapagliflozin (AstraZeneca, Wilmington, DE, USA) is approved as a treatment for T2DM in the European Union, USA, and other countries. In Phase III trials, dapagliflozin reduced  $A_{1C}$  (up to approximately  $-0.7\%$ , placebo-corrected), fasting plasma glucose (FPG, up to approximately  $-27$  mg/dL), and in most studies, body weight by 2–3 kg in patients with T2DM who were inadequately controlled with diet and exercise,<sup>75</sup> metformin,<sup>76,77</sup> glimepiride,<sup>78</sup> pioglitazone,<sup>79</sup> sitagliptin with and without metformin,<sup>80</sup> and insulin.<sup>81</sup> In addition, combination of dapagliflozin (5 or 10 mg/day) and metformin extended release as initial therapy in treatment-naïve patients was more effective than either drug alone in reducing  $A_{1C}$ ; dapagliflozin 10 mg alone was also noninferior to metformin.<sup>82</sup> Finally, in patients inadequately controlled with metformin, dapagliflozin ( $\leq 10$  mg/day) was noninferior to glipizide ( $\leq 20$  mg/day) in reducing  $A_{1C}$ .<sup>77</sup>

In patients with T2DM and moderate renal impairment (estimated GFR [eGFR] 30–59 mL/min/1.73 m<sup>2</sup>), mean decreases in  $A_{1C}$  were similar for placebo ( $-0.32\%$ ) and for dapagliflozin 5 mg/day ( $-0.41\%$ ) and 10 mg/day ( $-0.44\%$ ) after 24 weeks of treatment.<sup>83</sup> Although there was no significant effect on glycemic parameters in these patients, a mean reduction from baseline in body weight was observed with dapagliflozin 5 mg/day ( $-1.3$  kg) and 10 mg/day ( $-1.7$  kg) versus an increase (0.7 kg) with placebo.

In a pooled analysis of 12 Phase II/III trials, dapagliflozin 10 mg/day reduced systolic BP from baseline by  $-4.4$  mmHg and diastolic BP by  $-2.1$  mmHg compared with changes of  $-0.9$  mmHg in systolic BP and  $-0.5$  mmHg in diastolic BP with placebo.<sup>84</sup> Dapagliflozin treatment was associated with significant weight reduction of up to 3 kg over 24 weeks.<sup>76,78,79,81</sup> The reduction in body weight with dapagliflozin is largely the result of a reduction in body fat.<sup>71</sup> The positive effects of dapagliflozin on hyperglycemia and body weight were sustained for up to two years when added to insulin<sup>85</sup> or metformin therapy.<sup>86,87</sup>

Dapagliflozin was generally well tolerated, and adverse events were balanced across treatment groups.<sup>75–79,81</sup> There was a low incidence of hypoglycemia when dapagliflozin was used as monotherapy<sup>75</sup> or as add-on to metformin,<sup>76,77</sup> pioglitazone,<sup>79</sup> or sitagliptin.<sup>80</sup> The proportion of patients with hypoglycemia was higher in the dapagliflozin groups than in the placebo groups when added to glimepiride<sup>78</sup> or insulin therapy,<sup>81</sup> and was significantly lower compared with glipizide.<sup>77</sup>

In a 12-week randomized, double-blind study in patients with T2DM and normal renal function, dapagliflozin

10 mg/day reduced the measured GFR from baseline by  $-10.8\%$  compared with  $-2.9\%$  with placebo.<sup>88</sup> Mean eGFR decreased from baseline up to week 2 and tended to return toward baseline by 12 weeks. In an analysis of 12 randomized placebo-controlled trials involving more than 4,000 patients with preserved renal function, dapagliflozin was associated with a reduction in eGFR at week 1 that slowly returned to baseline by week 24 and was maintained at that level for 2 years.<sup>89</sup> The acute reductions in GFR may be due to reversible hemodynamic effects such as a decrease in BP or plasma volume as a result of the modest diuretic action of dapagliflozin.<sup>88</sup> Because of the reduced efficacy in patients with renal impairment, dapagliflozin is not recommended in patients with moderate to severe renal impairment (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>).<sup>84</sup>

In data pooled from 12 randomized, placebo-controlled trials, dapagliflozin 2.5, 5, or 10 mg once daily was accompanied by an increased risk of vulvovaginitis or balanitis (4.1%–5.7% versus 0.9% with placebo).<sup>90</sup> Diagnosed urinary tract infections occurred more frequently with dapagliflozin 5 mg (5.7%) and 10 mg (4.3%) compared with placebo (3.7%).<sup>91</sup>

## Canagliflozin

Canagliflozin (Janssen Pharmaceuticals, Inc., Titusville, NJ, USA) is approved for the treatment of T2DM in the USA, European Union, and other countries. In Phase III trials, treatment with canagliflozin (100 and 300 mg/day) for 26 or 52 weeks increased glucose excretion and decreased  $A_{1C}$  (maximum change versus placebo or comparator  $-1.16\%$ ) and FPG ( $-43$  mg/dL) in patients with T2DM when used as monotherapy,<sup>92</sup> as add-on therapy to metformin,<sup>93</sup> or as add-on to metformin and sulfonylurea.<sup>94</sup> In patients stabilized on metformin, canagliflozin 100 mg/day was noninferior (mean difference  $-0.01\%$ ; 95% confidence interval (CI)  $-0.11\%$ , 0.09%) and 300 mg/day was superior (mean difference  $-0.12\%$ ; 95% CI  $-0.22\%$ ,  $-0.02\%$ ) to glimepiride (6 to 8 mg/day) in reducing  $A_{1C}$ .<sup>93</sup> Absolute decreases in body weight of up to 4.2 kg after 52 weeks of therapy with 300 mg/day have been reported.<sup>93</sup> Canagliflozin (300 mg/day) as add-on to metformin and sulfonylurea was more effective than sitagliptin (100 mg/day) in reducing body weight, FPG, and systolic BP.<sup>95</sup>

In patients with T2DM and chronic kidney disease (eGFR  $\geq 30$  and  $< 50$  mL/min/1.73 m<sup>2</sup>), treatment with canagliflozin for 26 weeks reduced  $A_{1C}$  from baseline by  $-0.33\%$  with 100 mg/day and by  $-0.44\%$  with 300 mg/day compared with  $-0.03\%$  with placebo.<sup>96</sup> Transient decreases in eGFR ( $-4$  to  $-6$  mL/min/1.73 m<sup>2</sup>) with canagliflozin were observed

at 3 weeks and trended toward baseline at 26 weeks. As expected, based on the mechanism of action, these reductions in  $A_{1C}$  in patients with impaired renal function were less than those reported in patients with normal renal function.<sup>92–95,97</sup>

In addition to inhibiting SGLT2, canagliflozin is a weak inhibitor of SGLT1, the transporter responsible for intestinal glucose absorption.<sup>98</sup> In healthy individuals, canagliflozin reduced postprandial plasma glucose and insulin and delayed the appearance of oral glucose in plasma following a mixed-meal tolerance test.<sup>99</sup> These results suggest that canagliflozin reduces postprandial glucose and insulin by increasing renal glucose excretion via SGLT2 inhibition and by delaying the intestinal absorption of glucose, possibly by inhibiting SGLT1.

An increase in symptomatic urinary tract infections<sup>92,93,96</sup> and genital infections<sup>92–94,96</sup> was observed with canagliflozin. In addition, canagliflozin was associated with a modest increase in bone fractures and a dose-dependent increase in low-density lipoprotein cholesterol.<sup>100</sup>

In patients with T2DM without kidney disease (eGFR >55 mL/min/1.73 m<sup>2</sup>), canagliflozin caused a small initial decrease in eGFR that was stable up to 52 weeks.<sup>93</sup> In an analysis of pooled data from four randomized, placebo-controlled trials, canagliflozin caused early transient decreases in eGFR that remained stable or were attenuated over the course of 26 weeks.<sup>101</sup> The changes in eGFR with canagliflozin 100 and 300 mg/day versus placebo were –1.6% and –3.0% versus –0.6% in patients <65 years of age and –2.6%, and –2.9% versus –0.4% in patients ≥65 years of age. Canagliflozin should not be used in patients with eGFR <45 mL/min/1.73 m<sup>2</sup> and the dose is limited to 100 mg/day in patients with eGFR of 45–<60 mL/min/1.73 m<sup>2</sup>.<sup>102</sup>

### Empagliflozin

Empagliflozin (Boehringer Ingelheim, Ingelheim, Germany, and Eli Lilly, Indianapolis, IN, USA) is approved in the European Union and USA. In patients with T2DM, empagliflozin increased glucose excretion and decreased FPG (up to –32 mg/dL, placebo-corrected) and  $A_{1C}$  (maximum of –0.69%) when used as monotherapy for 12 weeks,<sup>103</sup> as add-on to metformin for 12 weeks,<sup>104</sup> or as add-on to pioglitazone for 24 weeks.<sup>105</sup> As add-on therapy to metformin and sulfonylurea, placebo-corrected changes in  $A_{1C}$  and FPG after 24 weeks were –0.65% and –0.60% for empagliflozin 10 and 25 mg/day, respectively.<sup>106</sup> Decreases in body weight<sup>103–106</sup> and systolic BP<sup>106</sup> have also been reported. Improvements in

glycemic control and weight reduction were sustained for up to 90 weeks.<sup>107</sup> An increased risk of genital and urinary tract infections was observed with empagliflozin.<sup>103,104,106,107</sup>

### Ipragliflozin

Ipragliflozin (Astellas, Tokyo, Japan, and Kotobuki, Hanishina, Japan) is approved in Japan for the treatment of T2DM. In a 12-week dose-ranging study in patients with T2DM, ipragliflozin (12.5, 50, 150, and 300 mg/day) dose-dependently reduced  $A_{1C}$  by up to 0.81% (placebo-corrected) and body weight by up to 1.7 kg. A decrease in  $A_{1C}$  of –0.72% was seen with metformin.<sup>108</sup> In a similarly designed 12-week study in patients inadequately controlled on metformin (≥1,500 mg/day), ipragliflozin reduced  $A_{1C}$  by a maximum of –0.48% at 300 mg.<sup>109</sup> Urinary tract and genital infections, as well as episodes of hypoglycemia, were similar with ipragliflozin and placebo. In patients with impaired renal function ± T2DM, a single dose of ipragliflozin increased urinary glucose excretion in patients with mild (eGFR ≥60 to <90 mL/min/1.73 m<sup>2</sup>), moderate (eGFR ≥30 to <60 mL/min/1.73 m<sup>2</sup>), and severe (eGFR ≤15 to <30 mL/min/1.73 m<sup>2</sup>) renal impairment. However, absolute glucose excretion decreased as eGFR declined.<sup>110</sup>

Other SGLT2 inhibitors in earlier phases of clinical development that have been reported to have positive effects on glycemic parameters in patients with T2DM include luseogliflozin (Taisho, Tokyo, Japan),<sup>111</sup> tofogliflozin (Chugai/Roche, Tokyo, Japan),<sup>112</sup> ertugliflozin, (Pfizer, New York, NY, USA)<sup>113</sup> and the SGLT2/SGLT1 inhibitor LX4211 (Lexicon Pharmaceuticals, The Woodlands, TX, USA).<sup>114</sup>

## Receptor agonists

### GPR119 agonists

The G-protein-coupled receptor (GPR)119 is expressed predominantly in the pancreas (β cells) and gastrointestinal tract in humans.<sup>115</sup> Although the endogenous ligand for this receptor is unknown, stimulation with synthetic ligands results in increased release of insulin, GLP-1, and GIP.<sup>115</sup> A number of GPR119 agonists are in development for T2DM,<sup>116,117</sup> and published findings for JNJ-38431055 (Johnson & Johnson Research & Development, Inc., Raritan, NJ, USA) report that this agent caused an increase in post-meal GLP-1 and GIP in patients with T2DM and was not associated with hypoglycemia.<sup>118</sup>

### Free fatty acid receptor 1 activators

The free fatty acid receptor 1 (FFAR1, also known as GPR40) is expressed mainly in pancreatic β cells.<sup>119</sup> Activation of this



receptor results in fatty acid-induced glucose-stimulated insulin secretion. In a 12-week Phase II clinical trial, the FFAR1 activator TAK-875 (Takeda, Osaka, Japan) significantly reduced  $A_{1c}$ , compared with placebo, with no increase in hypoglycemia.<sup>120</sup>

### 11 $\beta$ -hydroxysteroid dehydrogenase type I inhibitors

Excess glucocorticoids can cause insulin resistance and, in some individuals, can lead to the development of T2DM.<sup>121</sup>

11 $\beta$ -hydroxysteroid dehydrogenase type I (11 $\beta$ -HSD1) converts inactive cortisone to cortisol in target tissues. Therefore, inhibition of this enzyme may improve insulin sensitivity. In a randomized, placebo-controlled Phase II study of overweight or obese patients with T2DM exhibiting inadequate glycemic control with metformin, an 11 $\beta$ -HSD1 inhibitor, INCB13739 (Incyte, Wilmington, DE, USA), significantly reduced  $A_{1c}$  and FPG compared with placebo.<sup>122</sup> Body weight, insulin resistance, and total cholesterol levels were also reduced with treatment.

## Summary and conclusion

The significant burden that T2DM imposes on individuals and society reinforces the need for achieving and maintaining glycemic control in these patients. The key to optimal control is early diagnosis and intensive treatment with a combination of agents that address the various pathophysiologic abnormalities in T2DM, thereby lowering fasting and postprandial glucose concentrations. Novel medications with mechanisms of action different from those of most existing drugs and with acceptable safety profiles (low rates of hypoglycemia and no weight gain) are essential for long-term glycemic control and for improving disease outcomes and comorbidities. SGLT2 inhibitors are the newest treatment option for T2DM. These agents improve glycemic control, lower fasting glucose concentrations, and promote weight loss. This new class of diabetes medication with a novel mechanism of action provides an additional option to improve glycemic control in patients with T2DM. Whether the investigational GPR119 agonists, FFAR1 activators, and 11 $\beta$ -HSD1 inhibitors are safe and effective treatments for T2DM will be determined by the results of longer-duration, Phase III studies.

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