Oral Hypoglycemic Agents

Subjects: Medicine, General & Internal

Contributor: Mohamed Omer Mahgoub , Ifrah Ismail Ali , Jennifer O. Adeghate , Kornélia Tekes , Huba Kalász , Ernest A. Adeghate

Diabetes mellitus (DM) is a chronic illness with an increasing global prevalence. More than 537 million cases of diabetes were reported worldwide in 2021, and the number is steadily increasing. The worldwide number of people suffering from DM is projected to reach 783 million in 2045. In 2021 alone, more than USD 966 billion was spent on the management of DM. Reduced physical activity due to urbanization is believed to be the major cause of the increase in the incidence of the disease, as it is associated with higher rates of obesity. Diabetes poses a risk for chronic complications such as nephropathy, angiopathy, neuropathy and retinopathy. Hence, the successful management of blood glucose is the cornerstone of DM therapy. The effective management of the hyperglycemia associated with type 2 diabetes includes physical exercise, diet and therapeutic interventions (insulin, biguanides, second generation sulfonylureas, glucagon-like peptide 1 agonists, dipeptidyl-peptidase 4 inhibitors, thiazolidinediones, amylin mimetics, meglitinides, α-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors and bile acid sequestrants).

type 2 diabetes mellitus | insulin resistance | diabetes complications | hypoglycemic agents | remission of type 2 diabetes

1. Introduction

Many drugs have been approved to lower DM-associated hyperglycemia. These agents include, but are not limited to, biguanides, sulfonylureas, thiazolidinediones, GLP-1 agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, inhibitors of α-glucosidase, amylin mimetic drugs, bile acid binding resins and sodium–glucose co-transporter (SGLT) inhibitors (**Figure 1**).

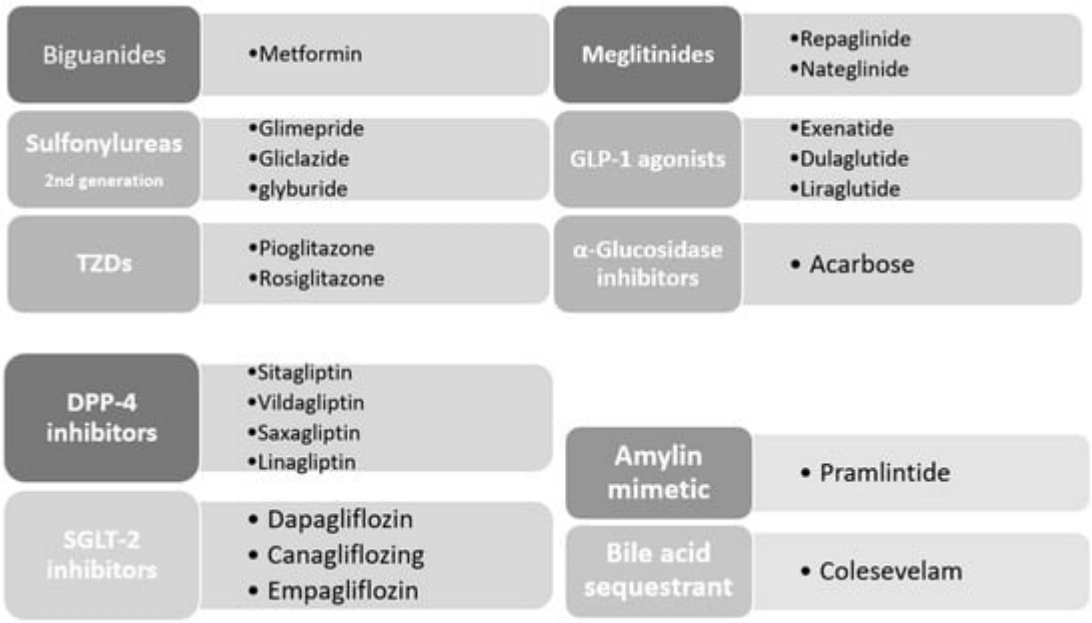

Figure 1. Classes of oral anti-diabetic agents and compounds approved by the American Diabetes Association (ADA).

2. Biguanides

Metformin is the only agent of this group used today. It is the most commonly used agent for T2DM and is accepted as a first-line agent [1]. It operates through the activation of AMP-dependent protein kinase (AMPK), which is activated when cellular energy stores are depleted under normal conditions [2]. The activation of AMPK leads to fatty acid oxidation and inhibits gluconeogenesis in the liver. Moreover, metformin can stimulate glucagon-like peptide-1 (GLP-1) secretion, which improves insulin sensitivity by enhancing the expression of insulin receptors and improving tyrosine kinase activity [3][4][5][6]. Furthermore, metformin can also lower plasma lipid levels and reduce the incidence of cardiovascular disease by acting on peroxisome proliferator-activated receptors (PPAR-αs) [3]. These molecular effects of metformin account for both the hypoglycemic and weight-reducing actions of metformin (**Figure 2**).

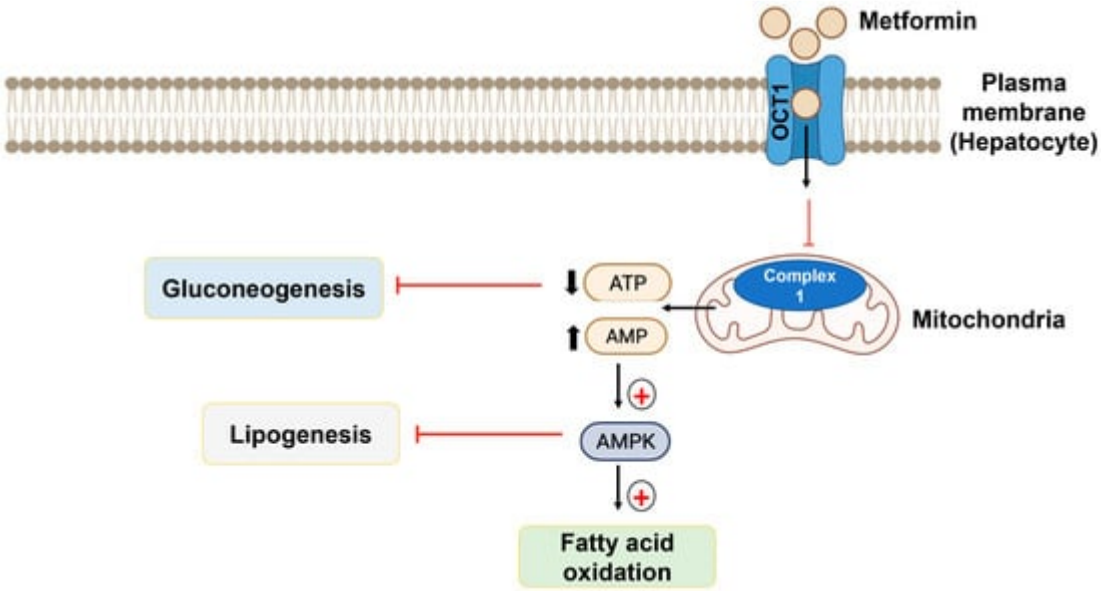

Figure 2. Mechanism of action of metformin. The binding of metformin with organic cation transporter-1 (OCT1) allows the metformin to reach the intracellular region, leading to the activation of AMPK, leading to the oxidation of fatty acid and the inhibition of gluconeogenesis in the liver.

Metformin can be used as a monotherapy and can also be found in combination with other hypoglycemic agents. Daily dosing varies depending on the formulation (immediate versus extended release), and the length of time on the medication but could range from 500 to 2550 mg daily. The recommended maximum dose of metformin is about 2550 mg daily [7][8].

The side effects caused by metformin mainly involve the gastrointestinal tract, including nausea, vomiting, diarrhea and abdominal discomfort [8]. Therefore, extended-release forms of metformin were developed to reduce the dosing frequency and eventually reduce these side effects. Moreover, the prolonged use of metformin is associated with folic acid and vitamin B12 deficiencies; as a result, monitoring the levels of both vitamins is needed, especially in the elderly [5][9]. Metformin should also be administered with caution and in low doses in patients with heart failure and renal failure as this category of patients have an increased risk of experiencing lactic acidosis, which is considered the most serious side effect of metformin [10]. The advantages and disadvantages of metformin are depicted in **Table 1**.

Table 1. Advantages and disadvantages of metformin.

Daily Dosage	Advantages	Side Effects	Contraindications
• 500–2550 mg (depending on immediate vs. extended-release formulations)	• Weight loss • Inexpensive	• Diarrhea • Vomiting • Dyspepsia	• Renal disease • Heart failure • Liver disease

Daily Dosage	Advantages	Side Effects	Contraindications
		• Flatulence • Metallic taste • Lactic acidosis	• Hypoxic pulmonary disease

3. Sulfonylureas

Sulfonylureas (SUs) are classified into first and second-generation agents. Due to their frequent dosing and higher risk of hypoglycemia, the first-generation drugs tolbutamide and tolzamide are no longer used clinically [11]. The second-generation agents, such as glibenclamide, gliclazide and glimepiride, are still in use, and some are available in extended-release formulations [9][12]. They exert their effect through the blockade of ATP-sensitive potassium channels found on the pancreatic β-cells, leading to cell depolarization, increasing cellular levels of calcium and enhancing the secretion of insulin, hence the name “insulin secretagogue” (**Figure 3**). In addition, SUs can also reduce the production of fatty acids and decrease insulin clearance 119. Due to their high efficacy in reducing HbA1c by up to 1–1.5% as and their cost-effectiveness, SUs are considered a second-line therapy and are currently used by 50–80% of diabetic patients worldwide [13][14]. However, prolonged use of these agents reduces their effectiveness. This may be due to progressive β-cell failure or an alteration in the drug’s metabolism.

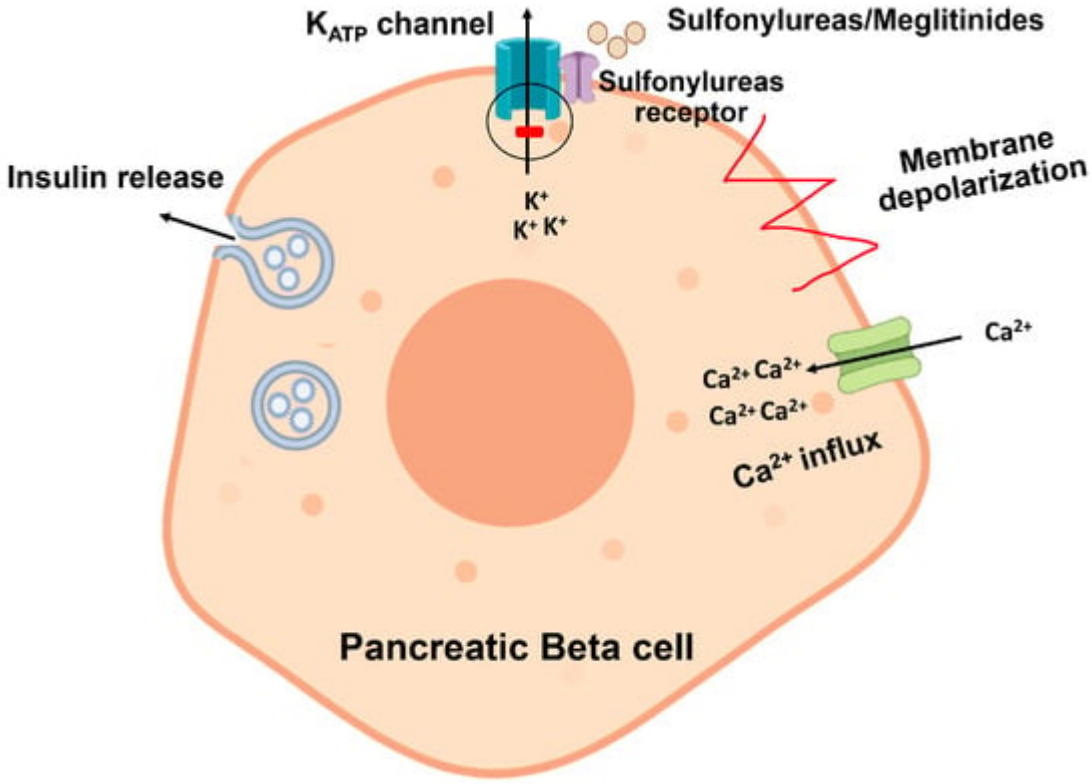

Figure 3. Sulfonylureas bind with the sulfonylurea receptor on the plasma membrane of pancreatic beta cells to block ATP-sensitive potassium channels. This leads to cell depolarization and subsequent increase in calcium-induced insulin release.

The major side effect seen with an SU is a weight gain of 1–3 kg. As a result, metformin is provided to patients on SU to reverse weight gain [9][15][16]. Hypoglycemia is also a common side effect, especially with glibenclamide and glimepiride; however, newer agents such as gliclazide have a lower tendency to cause this effect [8].

Sulfonylurea-induced hypoglycemia may be caused by decreased renal excretion, hepatic metabolism or displacement from protein-binding sites, which typically occurs in patients with renal/hepatic failure or when co-administered with CYP450 enzyme inhibitors such as aspirin and allopurinol [17]. The advantages and disadvantages of SUs are presented in **Table 2**.

Table 2. Advantages and disadvantages of sulfonylureas.

Daily Dosage	Advantages	Side Effects	Contraindications
• Glibenclamide (1.25–20 mg) • Glimepiride (1–8 mg) • Gliclazide (30–120 mg)	• Rapid effectiveness	• Weight gain • Hypoglycemia • GI distress • Dizziness	• Pregnancy • Ketoacidosis

4. Meglitinides

Meglitinides, including repaglinide and nateglinide, belong to another class of insulin secretagogue agents that exert their action by blocking the ATP-sensitive potassium channels in pancreatic β-cells [18] (**Figure 4**). Unlike SUs, meglitinides have a rapid onset but a short duration of action. These features make them suitable for patients with inconsistent meal times and those who develop rapid postprandial hyperglycemia [19][20][21]. The advantages and disadvantages of meglitinides are shown in **Table 3**.

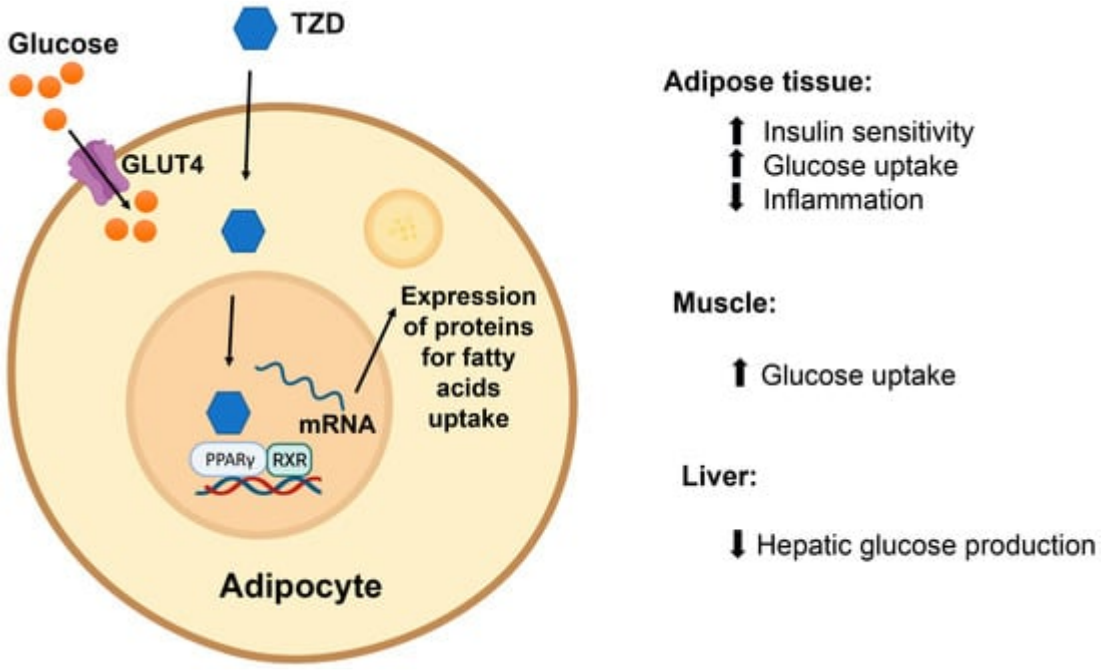

Figure 4. Thiazolidinediones (TZDs) activate PPARγ receptors in adipose tissue to enhance the uptake of circulating fatty acids into adipocytes.

Table 3. Advantages and disadvantages of meglitinides.

Daily Dosage	Advantages	Side Effects	Contraindications
• Repaglinide (0.5–4 mg) • Nateglinide (60–120 mg)	• Ideal for postprandial glucose increase • Ideal for patients with irregular meal schedule	• Weight gain • Hypoglycemia	• Pregnancy • Hypersensitivity • Co-administration of gemfibrozil with repaglinide

5. Thiazolidinediones

Two agents from this class are currently used clinically: pioglitazone and rosiglitazone. This pair of agents exerts its hypoglycemic effect by activating PPARγ receptors. PPARγ receptors are expressed primarily in adipose tissue, with lower expression in skeletal muscle, liver, pancreatic β-cells, the central nervous system (CNS) and vascular endothelial cells [10][20][21]. The primary effect of thiazolidinediones (TZDs) is believed to be through the activation of PPARγ receptors in adipose tissue, which promotes the uptake of circulating fatty acids into fat cells, thereby increasing insulin sensitivity.

Moreover, activation of this receptor in skeletal muscle and the liver also contribute to TZD action as they increase glucose uptake and reduce glucose production in both organs, respectively. TZD can cause a 0.5–1.4% reduction

in HbA1c, and clinical trials showed a 10–15% reduction in plasma triglyceride levels [22][23]. In fact, this effect on the lipid profile is believed to be mediated through another isoform of PPAR receptors present in the liver, heart and skeletal muscles [24]. Furthermore, TZDs were also found to reduce the levels of inflammatory cytokines, such as tumor necrosis factor alpha, improving the function of pancreatic β-cells and increasing the levels of adiponectin, both of which are believed to contribute to their insulin-sensitizing effects [10].

The common side effects of TZDs include weight gain and edema. These are believed to occur because of the activation of PPARγ receptors in the CNS, which increases food intake [25]. Studies showed that TZDs can also increase the risk of bone fracture in women and caused a reduction in transaminases; therefore, they should be avoided in patients with liver disease. Rosiglitzone has also been associated with an increase in myocardial infarction incidence [26]. The advantages and disadvantages of TZDs are provided in **Table 4**.

Table 4. Advantages and disadvantages of thiazolidinediones.

Daily Dosage	Advantages	Side Effects	Contraindications
• Pioglitazone (15–45 mg) • Rosiglitazone (4–8 mg)	• Improve lipid metabolism	• Fluid retention • Weight gain • Bone loss	• Active liver disease • Patients with heart failure (Class III; IV)

5. Glucagon-like Peptide-1 (GLP-1) Agonists

Glucagon-like peptide-1 (GLP-1) is an incretin secreted from the distal ileum in response to nutrients such as proteins and carbohydrates [27][28][29]. Following its release, GLP-1 binds to its receptor, GLP-1R, which is expressed on the pancreatic β-cells, thereby activating a cascade of intracellular events that increases the release of insulin, inhibits the release of glucagon, reduces food intake by causing satiety, delays food emptying and normalizes both postprandial and fasting insulin secretion [30] (**Figure 5**).

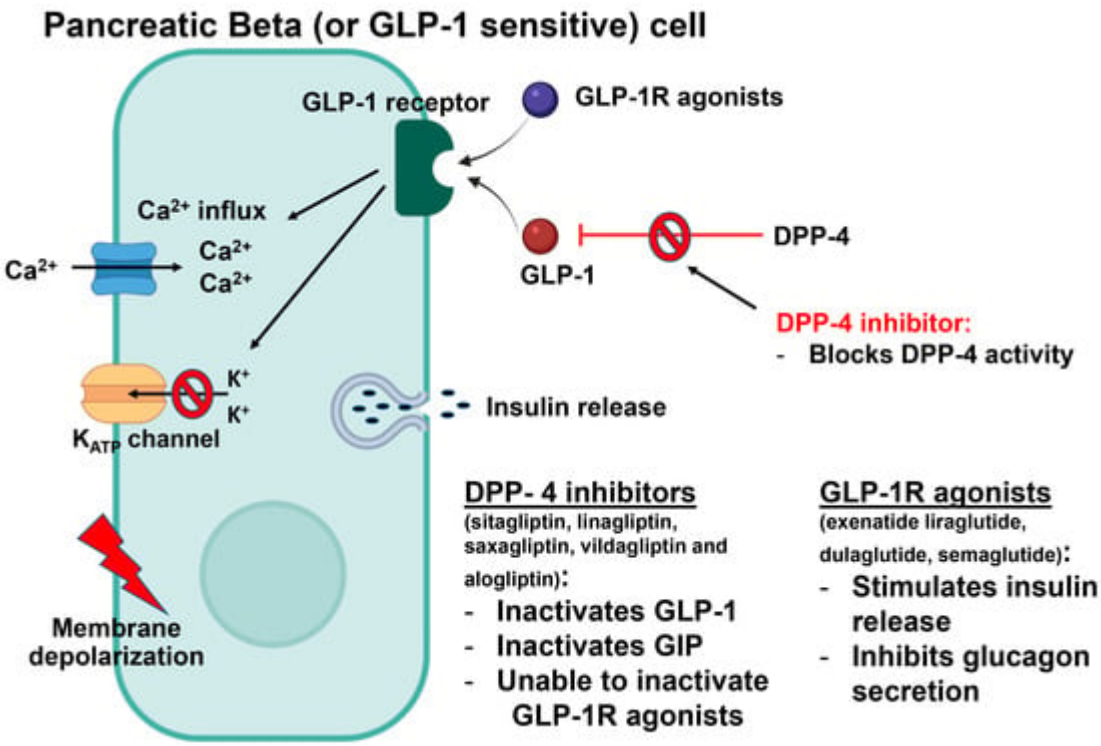

Figure 5. GLP-1 binds to GLP-1R and activates a cascade of intracellular events, leading to insulin release and the inhibition of glucagon production.

Patients with DM were found to have a significant reduction in the levels of GLP-1, which is believed to occur due to a reduction in the expression of GLP-1 receptors in the pancreas [31][32] or an enhancement of DPP-4 activity [32]. Due to its potent insulinotropic effects, restoring the activity of GLP-1 arose as a potential target for researchers and pharmaceutical companies. As a result, several GLP-1 agonists have been developed and used clinically in the management of T2DM [33][34][35], including exenatide, liraglutide and dulaglutide [8][10]. These molecules are administered subcutaneously and have various pharmacokinetic properties accounting for the differences in dosing. The majority of side effects associated with the administration of these compounds involve the GI tract, and this includes diarrhea, nausea and vomiting. In addition, some patients reported abscesses, cellulitis formation and even tissue necrosis at the site of injection [34][36]. The risk for hypoglycemia is low unless they are used in combination with insulin or sulfonylureas. The advantages and disadvantages of incretins are provided in **Table 5**.

Table 5. Advantages and disadvantages of incretins.

Weekly Dosage	Advantages	Side Effects	Contraindications
• Exenatide (2 mg) • Liraglutide (0.6–3.0 mg)	• Low hypoglycemia • Weight loss • Lowering blood pressure and cardiovascular disease	• Nausea	• Pancreatitis • Renal impairment

Weekly Dosage	Advantages	Side Effects	Contraindications
• Dulaglutide (0.75–1.5 mg) • Semaglutide (0.25–0.5 mg)			

ic and the the ability to improve cardiovascular function [37].

7. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 is a serine protease that is expressed on endothelial cells and T-lymphocytes and in a free-circulating form. Its main function is the inactivation of the glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) produced in the intestines [38][39]. These two hormones are known as incretins, and they play an essential metabolic role in augmenting the secretion of insulin, inhibiting glucagon secretion and reducing the absorption of nutrients [33][40]. By inhibiting this enzyme, DPP-4 inhibitors are considered oral hypoglycemic agents that are used widely in the management of DM (**Figure 6**).

Several DPP-4 inhibitors are available nowadays, such as sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin. They can be used alone or in combination, and studies have shown a 0.48–0.6% reduction in HbA1c and >95% decrease in the activity of DPP-4 for 12 h [33][38].

Unlike the previously mentioned antidiabetic agents, DPP-4 inhibitors have no effect on insulin sensitivity or secretion; as a result, weight gain is not an adverse effect of gliptins [16][35][41]. Sitagliptin, saxagliptin and vildagliptin are excreted renally; therefore, dose adjustment is required for diabetic patients with moderate to severe renal disease. Linagliptin, on the other hand, is excreted by the enterohepatic system, so it can be used as the agent of choice in renal impairment [42].

Although they cause minimal to no weight gain and have a low incidence of hypoglycemia, DPP-4 inhibitors are associated with other side effects such as nasopharyngitis, upper respiratory tract infections and headaches. In addition, these agents were found to cause pancreatitis and hepatic dysfunction after prolonged use [43]. The advantages and disadvantages of incretins are depicted in **Table 6**.

Table 6. Advantages and disadvantages of Dipeptidyl peptidase-4 (DPP-4) inhibitors.

Daily Dosage	Advantages	Side Effects	Contraindications
• Sitagliptin (50–100 mg) • Saxagliptin (2.5–5 mg) • Vildagliptin (50–100 mg)	• Weight loss	• Hypoglycemia • Pancreatitis • GI distress	• Pregnancy • Pancreatitis • Heart failure

Daily Dosage	Advantages	Side Effects	Contraindications
• Linagliptin (5 mg)		• Flu-like symptoms • Joint pain	• Angioedema

8. α-Glucosidase Inhibitors

Acarbose and miglitol are two agents of this class that are available and used clinically. α-glucosidase is an enzyme responsible for the breakdown of oligosaccharides into monosaccharides, and inhibiting it causes a reduction in intestinal glucose absorption by delaying the digestion of carbohydrates [44][45][46][47][48]. Moreover, these compounds were also reported to augment the release of GLP-1, which also contributes to their HbA1c-lowering activity (0.5–0.8%) [8][20]. The major side effects associated with this class are flatulence, diarrhea and abdominal pain [8]. The advantages and disadvantages of α-glucosidase inhibitors are provided in **Table 7**.

Table 7. Advantages and disadvantages of α-Glucosidase inhibitors.

Daily Dosage.	Advantages	Side Effects	Contraindications
• Acarbose (25–300 mg)	• Minimal risk of hypoglycemia	• GI distress	• Liver cirrhosis • Colonic ulceration • Inflammatory bowel disease

9. Amylin Mimetic

Amylin is a pancreatic hormone co-secreted with insulin from β-cells in the pancreas, and it acts by reducing the secretion of glucagon, delaying gastric emptying, and inducing satiety [25][49][50]. (**Figure 6**). Pramlintide is the only available amylin mimetic approved for use by the Food and Drug Administration. It is administered subcutaneously, and it is used in both T1DM and T2DM [51][52]. The advantages and disadvantages of amylin are provided in **Table 8**.

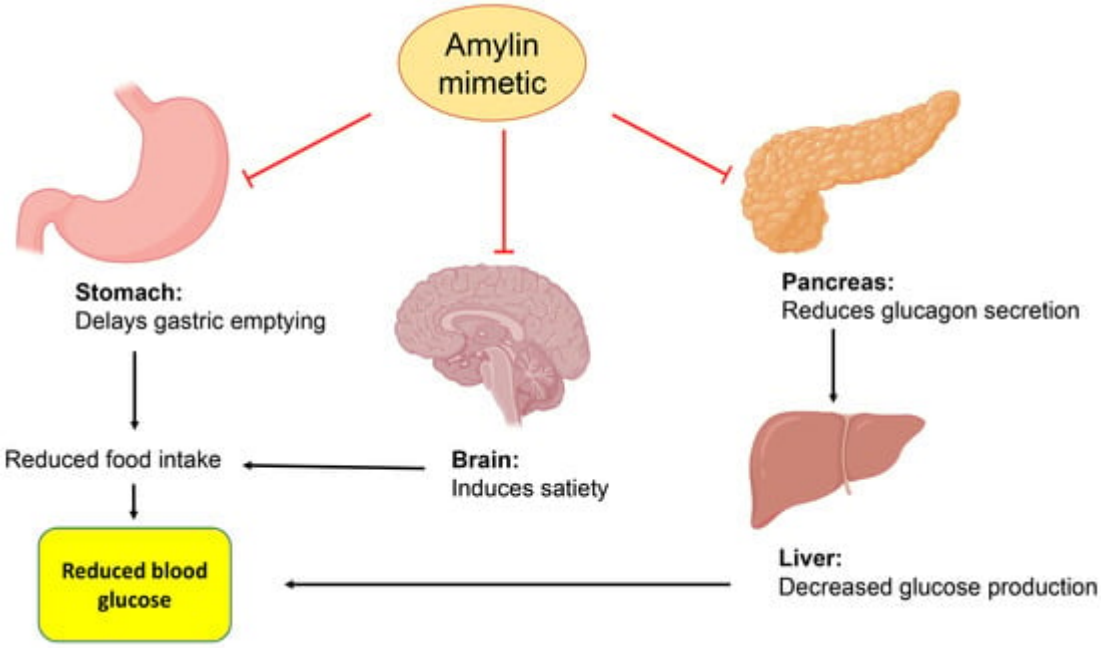

Figure 6. Amylin delays gastric emptying, increases satiety, and reduces glucagon secretion.

Table 8. Advantages and disadvantages of Amylin mimetics.

Daily Dosage.	Advantages	Side Effects	Contraindications
• Pramlinitide (30–60 µg)	• Weight loss	• Nausea	• Gastroparesis • Asymptomatic hypoglycemia

10. Bile Acid Binding Resins

Colesevelam is the only agent in this class of hypoglycemic agents. Although it does not have a direct effect on insulin secretion and/or sensitivity, the glucose-lowering mechanism of bile acid sequestrants is mostly unknown [53][54]. It is known, however, that colesevelam can reverse dyslipidemia, which is recognized as an exacerbating factor in T2DM. Current data suggest that colesevelam alone can produce a 0.5% reduction in HbA1c and a 13–17% reduction in low-density lipoproteins (LDL) [55]. A lack of systemic side effects makes this a good adjunct medication for managing T2DM (**Figure 7**).

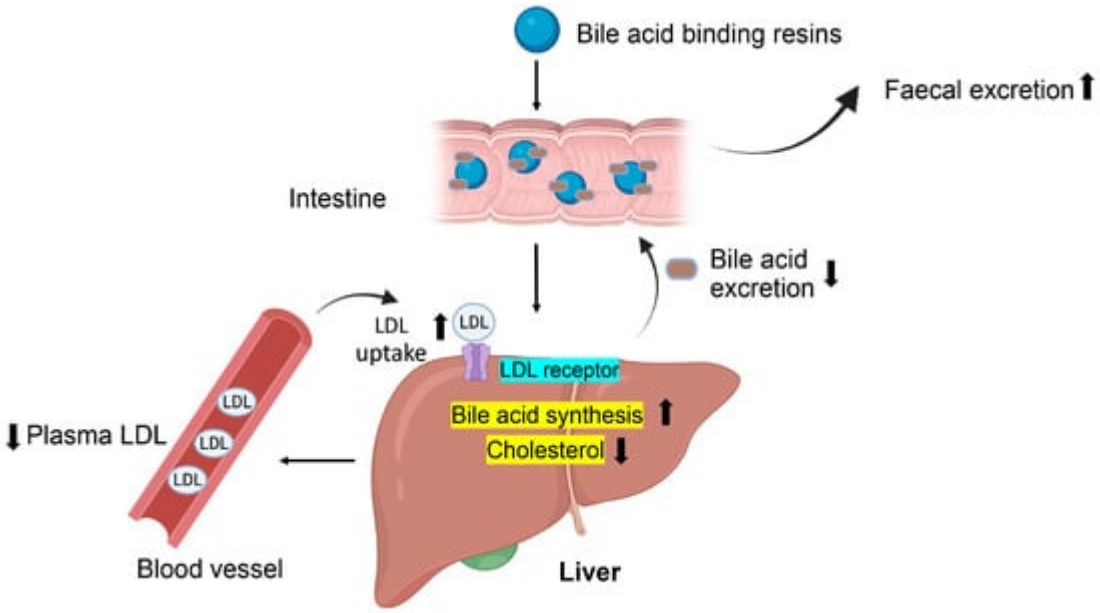

Figure 7. Bile acid binding resins stimulate LDL-receptors on hepatocytes to enhance the uptake of LDL proteins from blood circulation.

11. Sodium–Glucose Co-Transporter (SGLT) Inhibitors

This is a newer class of antidiabetics that was introduced clinically in 2013, with canagliflozin being approved by the Food and Drug Administration (FDA) [56][57]. These molecules exert their action on the renal sodium–glucose co-transporter-2 (SGLT2) molecule, which is responsible for glucose reabsorption in the proximal renal tubules [58] (**Figure 8**).

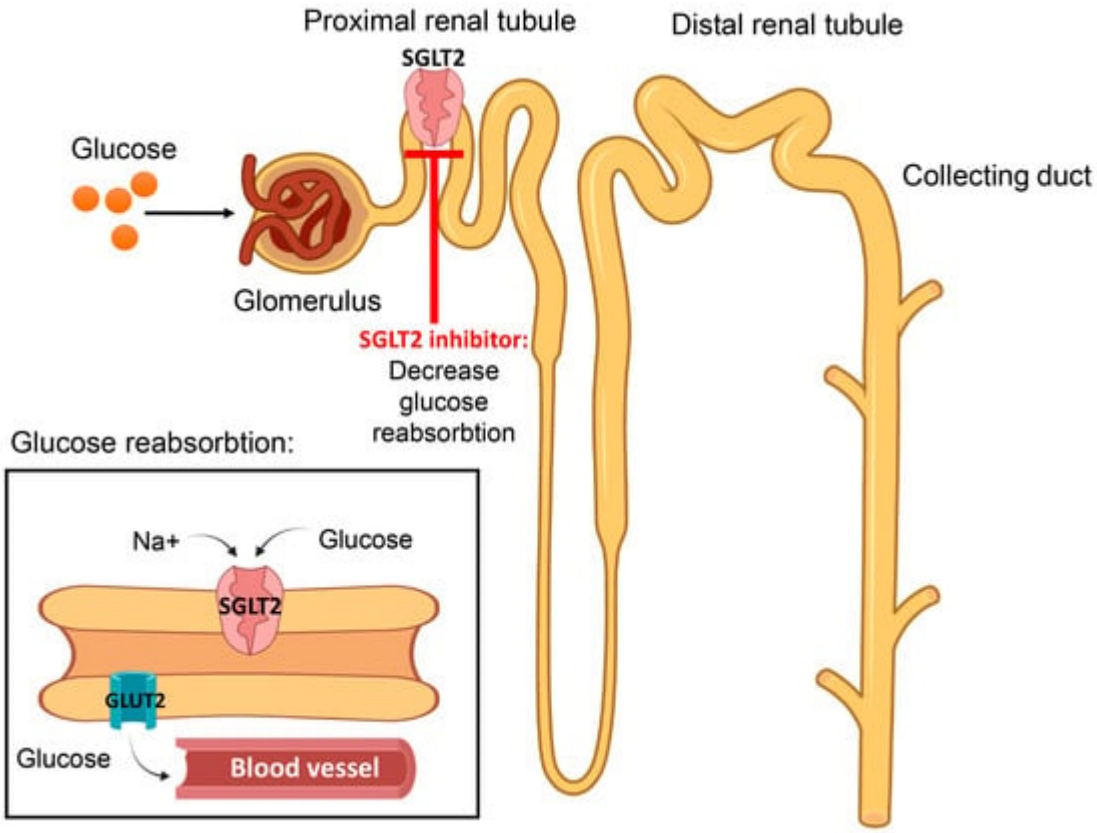

Figure 8. Sodium–glucose co-transporter (SGLT) inhibitors prevent the reabsorption of glucose from the proximal convoluted tubule, thereby reducing blood glucose level by increasing excretion.

This novel agent stimulates glucose excretion and has also been shown to have weight loss effects with minimal hypoglycemia [59][60]. In fact, canagliflozin was reported to cause a significant reduction in HbA1c of 0.77–1.03% [61], and dapagliflozin produced similar results after both short- and long-term treatments [62]. Another type of SGLT exists which is found in the intestines and the proximal convoluted tubules of the kidneys [63][64]. Although SGLT2 is responsible for the reabsorption of 90% of glucose filtered via glomeruli, diabetic patients with declining renal function may respond less to SGLT2 inhibitors, making SGLT1 inhibitors a better option for treatment [64]. Furthermore, dual SGLT1 and SGLT2 inhibitors such as sotagliflozin and licogliflozin are currently being investigated and are expected to have an agonistic hyoyglycemic effect while enhancing GLP-1 release from the intestines [64]. Currently, three types of SGLT2 inhibitors have been approved for use in the United States, including dapagliflozin, empagliflozin and the prototype SGLT2 inhibitor canagliflozin [60], while sotagliflozin is under investigation. In general, these agents have a good pharmacokinetic profile, including excellent oral bioavailability, a long half-life and limited renal excretion; however, they increase the risk for genital and urinary tract infections and orthostatic hypotension [42].

References

1. Inzucchi, S.E.; Bergenstal, R.M.; Buse, J.B.; Diamant, M.; Ferrannini, E.; Nauck, M.; Peters, A.L.; Tsapas, A.; Wender, R.; Matthews, D.R. 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.
2. Rena, G.; Hardie, D.G.; Pearson, E.R. The mechanisms of action of metformin. Diabetologia 2017, 60, 1577–1585.
3. Chatterjee, S.; Davies, M.J. Current management of diabetes mellitus and future directions in care. Postgrad. Med. J. 2015, 91, 612–621.
4. Leroith, D.; Biessels, G.J.; Braithwaite, S.S.; Casanueva, F.F.; Draznin, B.; Halter, J.B.; Hirsch, I.B.; McDonnell, M.; Molitch, M.E.E.; Murad, M.H.; et al. Treatment of diabetes in older adults: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 2019, 104, 1520–1574.
5. American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care 2000, 23 (Suppl. 1), S43–S46.
6. Balakumar, P.; Maung-U, K.; Jagadeesh, G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacol. Res. 2016, 113 Pt 1, 600–609.
7. Lim, P.C.; Chong, C.P. What’s next after metformin? focus on sulphonylurea: Add-on or combination therapy. Pharm. Pract. 2015, 13, 606.
8. Marín-Peñalver, J.J.; Martín-Timón, I.; Sevillano-Collantes, C.; Del Cañizo-Gómez, F.J. Update on the treatment of type 2 diabetes mellitus. World J. Diabetes 2016, 7, 354–395.
9. Tran, L.; Zielinski, A.; Roach, A.H.; Jende, J.A.; Householder, A.M.; Cole, E.E.; Atway, S.A.; Amornyard, M.; Accursi, M.L.; Shieh, S.W.; et al. Pharmacologic treatment of type 2 diabetes: Oral medications. Ann. Pharmacother. 2015, 49, 540–556.
10. Chaudhury, A.; Duvoor, C.; Reddy Dendi, V.S.; Kraleti, S.; Chada, A.; Ravilla, R.; Marco, A.; Shekhawat, N.S.; Montales, M.T.; Kuriakose, K.; et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front. Endocrinol. 2017, 8, 6.
11. Olokoba, A.B.; Obateru, O.A.; Olokoba, L.B. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Med. J. 2012, 27, 269–273.
12. Eldor, R.; Raz, I. Diabetes therapy--focus on Asia: Second-line therapy debate: Insulin/secretagogues. Diabetes/Metab. Res. Rev. 2012, 28, 85–89.
13. Holman, R.R.; Paul, S.K.; Bethel, M.A.; Matthews, D.R.; Neil, H.A. 10-year follow-up of intensive glucose control in type 2 diabetes. N. Engl. J. Med. 2008, 359, 1577–1589.
14. Lau, D.C.; Teoh, H. Impact of Current and Emerging Glucose-Lowering Drugs on Body Weight in Type 2 Diabetes. Can. J. Diabetes 2015, 39, S148–S154.

15. Nathan, D.M. Diabetes: Advances in Diagnosis and Treatment. JAMA 2015, 314, 1052–1062.
16. Nauck, M.A.; Meininger, G.; Sheng, D.; Terranella, L.; Stein, P.P. Sitagliptin Study 024 Group Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial. Diabetes Obes. Metab. 2007, 9, 194–205.
17. Scott, L.J. Repaglinide: A review of its use in type 2 diabetes mellitus. Drugs 2012, 72, 249–272.
18. Kaufman, F.R. Type 1 diabetes mellitus. Pediatr. Rev. 2003, 24, 291–300.
19. Tahrani, A.A.; Bailey, C.J.; Del Prato, S.; Barnett, A.H. Management of type 2 diabetes: New and future developments in treatment. Lancet 2011, 378, 182–197.
20. Lorenzati, B.; Zucco, C.; Miglietta, S.; Lamberti, F.; Bruno, G. Oral Hypoglycemic Drugs: Pathophysiological Basis of Their Mechanism of ActionOral Hypoglycemic Drugs: Pathophysiological Basis of Their Mechanism of Action. Pharmaceuticals 2010, 3, 3005–3020.
21. Skliros, N.P.; Vlachopoulos, C.; Tousoulis, D. Treatment of diabetes: Crossing to the other side. Hell. J. Cardiol. 2016, 57, 304–310.
22. Rosenfeld, C.R. Insulin therapy in type 2 diabetes mellitus: History drives patient care toward a better future. J. Am. Osteopat. Assoc. 2013, 113, S4–S5.
23. Jermendy, G. Intensive insulin therapy in type 2 diabetes mellitus. Orv. Hetil. 2012, 153, 1487–1493.
24. Jung, Y.; Cao, Y.; Paudel, S.; Yoon, G.; Cheon, S.H.; Bae, G.U.; Jin, L.T.; Kim, Y.K.; Kim, S.-N. Antidiabetic effect of SN158 through PPARalpha/gamma dual activation in ob/ob mice. Chem. Biol. Interact. 2017, 268, 24–30.
25. Zhou, G.; Myers, R.; Li, Y.; Chen, Y.; Shen, X.; Fenyk-Melody, J.; Wu, M.; Ventre, J.; Doebber, T.; Fuji, N.; et al. Role of AMP-activated protein kinase in mechanism of metformin action. J. Clin. Investig. 2001, 108, 1167–1174.
26. Vieira, R.; Souto, S.B.; Sánchez-López, E.; López Machado, A.; Severino, P.; Jose, S.; Santini, A.; Fortuna, A.; García, M.L.; Silva, A.M.; et al. Sugar-Lowering Drugs for Type 2 Diabetes Mellitus and Metabolic Syndrome—Review of Classical and New Compounds: Part-I. Pharmaceuticals 2019, 12, 152.
27. Scheen, A.J. Dulaglutide for the treatment of type 2 diabetes. Expert Opin. Biol. Ther. 2017, 17, 485–496.
28. Wysham, C.H.; Lin, J.; Kuritzky, L. Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: Results of a meta-analysis. Postgrad. Med. 2017, 129, 1–10.

29. Zhou, M.; Mok, M.T.; Sun, H.; Chan, A.W.; Huang, Y.; Cheng, A.S.; Xu, G. The anti-diabetic drug exenatide, a glucagon-like peptide-1 receptor agonist, counteracts hepatocarcinogenesis through cAMP-PKA-EGFR-STAT3 axis. Oncogene 2017, 36, 4135–4149.
30. DeWitt, D.E.; Hirsch, I.B. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. JAMA 2003, 289, 2254–2264.
31. Setji, T.L.; Hong, B.D.; Feinglos, M.N. Technosphere insulin: Inhaled prandial insulin. Expert Opin. Biol. Ther. 2015, 16, 111–117.
32. Viollet, B.; Guigas, B.; Garcia, N.S.; Leclerc, J.; Foretz, M.; Andreelli, F. Cellular and molecular mechanisms of metformin: An overview. Clin. Sci. 2012, 122, 253–270.
33. Kosiborod, M.; Gause-Nilsson, I.; Xu, J.; Sonesson, C.; Johnsson, E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. J. Diabetes Complicat. 2017, 31, 1215–1221.
34. Cao, L.; Li, D.; Feng, P.; Li, L.; Xue, G.-F.; Li, G.; Hölscher, C. A novel dual GLP-1 and GIP incretin receptor agonist is neuroprotective in a mouse model of Parkinson's disease by reducing chronic inflammation in the brain. Neuroreport 2016, 27, 384–391.
35. Jermendy, G. Incretin-based antidiabetic treatment and diseases of the pancreas (pancreatitis, pancreas carcinoma). Orv. Hetil. 2016, 157, 523–528.
36. Garber, A.; Henry, R.; Ratner, R.; Garcia-Hernandez, P.A.; Rodriguez-Pattzi, H.; Olvera-Alvarez, I.; Hale, P.M.; Zdravkovic, M.; Bode, B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009, 373, 473–481.
37. Zhao, X.; Wang, M.; Wen, Z.; Lu, Z.; Cui, L.; Fu, C.; Xue, H.; Liu, Y.; Zhang, Y. GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Front. Endocrinol. 2021, 12, 721135.
38. Lotfy, M.; Singh, J.; Kalász, H.; Tekes, K.; Adeghate, E. Medicinal Chemistry and Applications of Incretins and DPP-4 Inhibitors in the Treatment of Type 2 Diabetes Mellitus. Open Med. Chem. J. 2011, 5 (Suppl. 2), 82–92, PMCID:PMC3174521.
39. Ishii, H.; Hayashino, Y.; Akai, Y.; Yabuta, M.; Tsujii, S. Dipeptidyl peptidase-4 inhibitors as preferable oral hypoglycemic agents in terms of treatment satisfaction: Results from a multicenter, 12-week, open label, randomized controlled study in Japan (PREFERENCE 4 study). J. Diabetes Investig. 2017, 9, 137–145.
40. Proks, P.; Reimann, F.; Green, N.; Gribble, F.; Ashcroft, F. Sulfonylurea Stimulation of Insulin Secretion. Diabetes 2002, 51 (Suppl. 1), S368–S376.
41. Nicholson, G.; Hall, G.M. Diabetes mellitus: New drugs for a new epidemic. Br. J. Anaesth. 2011, 107, 65–73.

42. Forst, T.; Uhlig-Laske, B.; Ring, A.; Graefe-Mody, U.; Friedrich, C.; Herbach, K.; Woerle, H.-J.; Dugi, K.A. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabete Med. 2010, 27, 1409–1419.
43. Amori, R.E.; Lau, J.; Pittas, A.G. Efficacy and safety of incretin therapy in type 2 diabetes: Systematic review and meta-analysis. JAMA 2007, 298, 194–206.
44. Chatterjee, S.; Khunti, K.; Davies, M.J. Type 2 diabetes. Lancet 2017, 389, 2239–2251.
45. Alberti, K.G.; Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabete Med. 1998, 15, 539–553.
46. Adeghate, E.A.; Kalász, H.; Al Jaberi, S.; Adeghate, J.; Tekes, K. Tackling type 2 diabetes-associated cardiovascular and renal comorbidities: A key challenge for drug development. Expert Opin. Investig. Drugs 2020, 30, 85–93.
47. Ryan, K.K.; Li, B.; Grayson, B.E.; Matter, E.K.; Woods, S.C.; Seeley, R.J. A role for central nervous system PPAR-gamma in the regulation of energy balance. Nat. Med. 2011, 17, 623–626.
48. Park, K.S.; Ciaraldi, T.P.; Abrams-Carter, L.; Mudaliar, S.; Nikoulina, S.E.; Henry, R.R. PPAR-gamma gene expression is elevated in skeletal muscle of obese and type II diabetic subjects. Diabetes 1997, 46, 1230–1234.
49. Shin, N.R.; Lee, J.C.; Lee, H.Y.; Kim, M.S.; Whon, T.W.; Lee, M.S.; Bae, J.W. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut 2014, 63, 727–735.
50. Song, R. Mechanism of Metformin: A Tale of Two Sites. Diabetes Care 2016, 39, 187–189.
51. Liu, M.; Hoskins, A.; Verma, N.; Bers, D.M.; Despa, S.; Despa, F. Amylin and diabetic cardiomyopathy—Amylin-induced sarcolemmal Ca2+ leak is independent of diabetic remodeling of myocardium. Biochim. Biophys. Acta-Mol. Basis Dis. 2018, 1864, 1923–1930.
52. Nyholm, B.; Brock, B.; Ørskov, L.; Schmitz, O. Amylin receptor agonists: A novel pharmacological approach in the management of insulin-treated diabetes mellitus. Expert Opin. Investig. Drugs 2001, 10, 1641–1652.
53. Hansen, M.; Sonne, D.P.; Mikkelsen, K.H.; Gluud, L.L.; Vilsbøll, T.; Knop, F.K. Effect of bile acid sequestrants on glycaemic control: Protocol for a systematic review with meta-analysis of randomised controlled trials. BMJ Open 2012, 2, e001803.
54. Hansen, M.; Sonne, D.P.; Mikkelsen, K.H.; Gluud, L.L.; Vilsbøll, T.; Knop, F.K. Bile acid sequestrants for glycemic control in patients with type 2 diabetes: A systematic review with meta-analysis of randomized controlled trials. J. Diabetes Complicat. 2017, 31, 918–927.

55. Brunetti, L.; Hermes-DeSantis, E.R. The Role of Colesevelam Hydrochloride in Hypercholesterolemia and Type 2 Diabetes Mellitus. Ann. Pharmacother. 2010, 44, 1196–1206.
56. Steen, O.; Goldenberg, R.M. The Role of Sodium-Glucose Cotransporter 2 Inhibitors in the Management of Type 2 Diabetes. Can. J. Diabetes 2017, 41, 517–523.
57. Weir, M.R. The kidney and type 2 diabetes mellitus: Therapeutic implications of SGLT2 inhibitors. Postgrad. Med. 2016, 128, 290–298.
58. Wong, J.; Tabet, E. The introduction of insulin in type 2 diabetes mellitus. Aust. Fam. Physician 2015, 44, 278–283.
59. Bailey, C.J.; Tahrani, A.A.; Barnett, A.H. Future glucose-lowering drugs for type 2 diabetes. Lancet Diabetes Endocrinol. 2016, 4, 350–359.
60. Scheen, A.J. Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs 2014, 75, 33–59.
61. Stenlöf, K.; Cefalu, W.T.; Kim, K.; Alba, M.; Usiskin, K.; Tong, C.; Canovatchel, W.; Meininger, G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes. Metab. 2013, 15, 372–382.
62. Bailey, C.J.; Gross, J.L.; Hennicken, D.; Iqbal, N.; Mansfield, T.A.; List, J.F. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: A randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013, 11, 43.
63. Bagnasco, A.; Di Giacomo, P.; Mora, R.D.R.D.; Catania, G.; Turci, C.; Rocco, G.; Sasso, L. Factors influencing self-management in patients with type 2 diabetes: A quantitative systematic review protocol. J. Adv. Nurs. 2013, 70, 187–200.
64. Adeghate, E.; Mohsin, S.; Adi, F.; Ahmed, F.; Yahya, A.; Kalász, H.; Tekes, K.; Adeghate, E.A. An update of SGLT1 and SGLT2 inhibitors in early phase diabetes-type 2 clinical trials. Expert Opin. Investig. Drugs 2019, 28, 811–820.

Retrieved from https://encyclopedia.pub/entry/history/show/103120