The origins of type 2 diabetes medications

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Abstract

The origins of diabetes medications provide an intriguing catalogue of clinical serendipity and scientific design. Use of insulin (beyond 1922) gave recognition to insulin resistance and the categorisation of type 2 diabetes (T2DM). The first sulphonylurea (carbutamide, 1956) emerged from its use as an antibacterial sulphonamide prone to cause hypoglycaemia, and biguanides were first used to treat diabetes in 1957 despite their glucose-lowering properties having been known since the 1920s. Alpha-glucosidase inhibitors arose from a screening programme for amylase inhibitors by Bayer in the 1970s and acarbose was introduced in 1990. The first thiazolidinedione (ciglitazone; not developed) was identified in a screening programme for triglyceride-lowering compounds by Takeda in the late 1970s and gave rise to pioglitazone (approved 1999), although first to market was troglitazone (from Warner Lambert 1997, withdrawn 2000). Exendin, an analogue of the incretin hormone glucagon-like peptide-1 (GLP-1), was identified in 1992 in the saliva of a lizard (Heloderma suspectum), and took until 2005 to be marketed as exenatide. To promote the efficacy of endogenous GLP-1, its rapid inactivation by the enzyme dipeptidylpeptidase-4 (DPP4) was blocked by clever molecular design of the first DPP4 inhibitors (vildagliptin and sitagliptin, approved in 2006). SGLT2 inhibitors are based on phlorizin, identified in apple tree bark (1835) and modified (2000) to avoid intestinal degradation: further modifications to increase selectivity against SGLT2 gave dapagliflozin and canagliflozin - approved 2012 and 2013, respectively, in Europe.

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Introduction

This brief account of the origins of diabetes medications is based on the John Wales Lecture, *Drugs by discovery and design*, delivered at the Association of British Clinical Diabetologists conference in September 2022. Nine classes of glucose-lowering agents are routinely used in the UK (table 1), and several further agents are indicated for glucose lowering in other regions.[1,2] Each drug class has an interesting history and has contributed to a succession of 'fashions' in the therapeutic management of hyperglycaemia in T2DM.

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Pre-insulin to insulin

Although there are many excellent accounts of the discovery and subsequent development of insulin, the pre-insulin era of research that focused attention on the pancreas is less well known.[3] Dating from the first description of the pancreatic islets by Paul Langerhans (Berlin) in 1869, a succession of innovative studies and astute observations (and some questionable findings) linked the pancreas with diabetes.[4-6] Indeed, while pre-insulin treatment of T1DM relied on starvation diets and herbal preparations, research studies in pancreatectomised animals investigated the use of pancreatic tissue and pancreatic extracts to reduce glucosuria and blood sugar, and prolong survival (table 2). The animal studies were acknowledged by Frederick Banting and Charles Best when describing their own work in Toronto, 1921-22: these studies undoubtedly fostered the enthusiasm of Banting, informed the choice of animal model and emphasized the need to co-opt the expertise of James Collip to refine the extraction process.[7]

Of particular note, a preliminary trial in the early 1900s by Georg Zuelzer (Berlin) achieved temporary respite with a pancreas extract injected into young diabetes patients.[8] The work of Nicolae Paulescu (Bucharest) also deserves its own footnote in pre-insulin research.[9] Paulescu had observed in 1916 that blood sugar was reduced in diabetic dogs after injection of pancreas extracts, but he was unable to proceed or publish his work until 1921 due to World War I. Paulescu and Zuelzer each applied for patents for their pancreas extraction processes, and voiced their discontent with the award of the Nobel prize to Banting (he shared his prize money with Best) and laboratory head John Macleod (he shared with Collip). Notwithstanding the wrangles over prizes, patents and accounts of who did what, we are reminded that even such a momentous discovery as that of insulin was built upon a pre-history of (often unrecognised) research by many individuals and groups, several just short of the definitive last few steps to successful clinical use.[4-6]

After the momentous achievements of Banting and colleagues in 1921-22, the extraction of bovine and porcine insulin was quickly refined and commercialised, and treatment became increasingly available.[3] However, the existence of insulin- insensitive presentations of diabetes (Harold Himsworth, 1936) then became recognised, and type 2 (maturity-onset) diabetes became distinguished from type 1 (juvenile-onset) diabetes (John Lister, 1951).[10,11] This distinction indicated that insulin was not

Table 1. Blood glucose-lowering agents used in the UK.*

Class with examples	Dose range mg/day (unless stated)	a. Glucose-lowering efficacy^ b. Hypo risk^ c. Weight^	Mode of action	Cautions, limitations and additional benefits
Oral				
Biguanide *Metformin (IR, SR/XR formulations)*	500-3000	a. High efficacy b. Low hypo risk c. Weight neutral	Counter insulin resistance ↓ hepatic glucose output ↑ glucose uptake and cycling	Check renal function. Interrupt if using contrast media. Avoid in renal or liver impairment, or any hypoxaemic state and history of lactic acidosis. Rare risk of lactic acidosis.Glucose-independent effects to reduce CV risk.
Sulphonylureas *Glibenclamide* *Gliclazide* *Gliclazide MR* *Glimepiride* *Glipizide* *Tolbutamide*	 2.5-20 40-320 30-100 1-6 2.5-20 500-3000	a. High efficacy b. Moderate hypo risk c. Weight gain	Initiate and potentiate insulin secretion (effect lasts 6–24 h depending on agent and dose)	Initial efficacy may wear-off after 6-12 months in some patients. Avoid in renal or liver impairment depending on agent. Risk of hypoglycaemia.
Meglitinides *Nateglinide* *Repaglinide*	 60-540 0.5-16	a. Intermediate efficacy b. Moderate hypo risk c. Weight gain	Initiate and potentiate insulin secretion (rapid effect, typically lasts < 6 h)	Avoid in liver impairment. Take with main meals
DPP4 inhibitors *Alogliptin* *Linagliptin* *Saxagliptin* *Sitagliptin* *Vildagliptin*	 6.25-25 5 2.5-5 25-100 50-100	a. Intermediate-high efficacy b. Low hypo risk c. Weight neutral	Prolong circulating half-lives of incretin hormones such as GLP-1	Discontinue if acute pancreatitis. Dose adjustment in renal impairment except linagliptin
Thiazolidinedione *Pioglitazone*	 15-45	a. High efficacy b. Low hypo risk c. Weight gain	↑ insulin sensitivity mainly via activation of PPARγ	Slow onset of action, risk of oedema. Increased risk of heart failure and bone fractures. Check liver enzymes and CV risk.
SGLT2 inhibitors *Canagliflozin* *Dapagliflozin* *Empagliflozin* *Ertugliflozin*	 100-300 5-10 10-25 5-15	a. Intermediate-high efficacy b. Low hypo risk c. Weight reduction	Inhibit renal SGLT2 to eliminate glucose via the urine.	Check for adequate renal function and hydration. Glucosuric effect: risk of genital and urinary infections. Can reduce blood pressure: evidence of reduced heart failure and chronic kidney disease.
Alpha-glucosidase inhibitors *Acarbose*	 50-600	a. Intermediate efficacy b. Low hypo risk c. Weight neutral	Slow carbohydrate digestion by competitive inhibition of intestinal glucosidases	Avoid if gastro-intestinal disorders. Side effect of flatulence
Subcutaneous injection				
GLP-1 receptor agonists *Dulaglutide* *Exenatide BD* *Exenatide QW* *Liraglutide* *Lixisenatide* *Semaglutide* *Semaglutide oral*	 0.75-1.5 QW 5-10 ug BD 2 QW 0.6-1.8 OD 10-20 ug OD 0.25-2 QW 3-14 mg/day	a. High efficacy b. Low hypo risk c. Weight reduction	Activate GLP-1 receptors to potentiate prandial insulin secretion, ↓ prandial glucagon secretion, delay gastric emptying and exert satiety effect	Initial nausea, titrate as appropriate. Discontinue if acute pancreatitis. Can reduce blood pressure: evidence of reduced CV risk and albuminuria.
Insulin Ultra-rapid acting: *Fiasp, Lyumjev* Rapid-acting: *Aspart, Glulisine, Lispro* Short-acting: *Actrapid, Humulin S, Insuman Rapid* Intermediate: *Insulatard, Humulin I* Long-acting: *Degludec, Detemir, Glargine* Biphasic (pre-mixed): *Humalog, Humulin M3, Novomix*	 For basal sc injections usually start at 0.1 or 0.2 units/kg body weight daily (ie 10 or 20 units per day for a person weighing 100kg). Titrate up dose to achieve target glycaemic control. For MDI give ~30-50% as basal, and remainder divided between meals	a. Very high efficacy b. High hypo risk c. Weight gain	↓ hepatic glucose output ↑ peripheral glucose uptake ↑ glucose metabolism ↓ lipolysis ↑ lipogenesis ↑ protein anabolism	Select regimen consistent with patient lifestyle and needs. Glucose monitoring required. Appropriate lifestyle adjustments. High risk of hypoglycemia

Continued on following page

Table 1. Blood glucose-lowering agents used in the UK continued.*

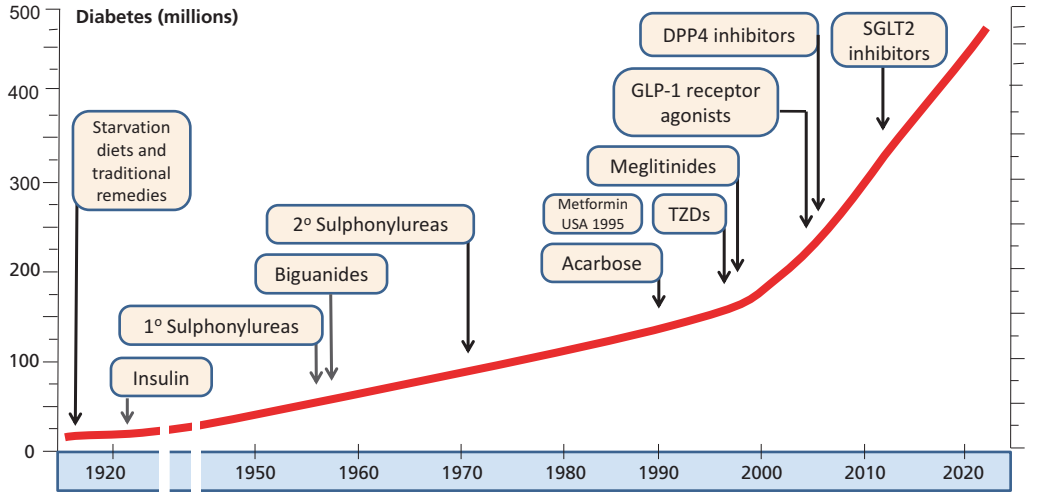
Key: BD, twice daily; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MDI, multiple daily insulin injections; OD, once daily; PPARγ , peroxisome proliferator-activated receptor-gamma; QW, once weekly; SGLT, sodium-glucose co-transporter; ↑ increase; ↓ decrease.

* Based on reference 1. Some agents are not available in all countries, eg. gliclazide is not available in USA. Some agents have different names and formulations in other countries, eg, glibenclamide is available as micronized glyburide in USA, and formulations of glipizide may vary between countries. Additional agents have indications as glucose-lowering agents outside Europe, eg. colesevelam (bile sequestrant), bromocriptine (dopamine D2 receptor agonist) and pramlintide (amylin analogue taken as subcutaneous injections before meals) have an indication for diabetes in the USA, and additional alpha-glucosidase inhibitors (miglitol and voglibose) are available in some countries outside the UK. Lixisenatide, pioglitazone and rosiglitazone are not available in some countries. Tirzepatide (GLP-1/GIP dual receptor agonist was approved in 2022 but was not marketed at the time of manuscript submission. Dosages of glucose-lowering agents may vary between countries, eg. a maximum recommended dose of metformin is 3000 mg/day in Europe and 2550 mg/day in USA. Exclusions, precautions and monitoring may also vary (eg. extent of renal impairment to contraindicate metformin varies between countries; TZDs are excluded for New York Heart Association (NYHA) categories I-IV in Europe but III-IV in USA). Fixed-dose combinations of several oral agents are widely available, eg single tablet combinations of metformin with a DPP4 inhibitor or SGLT2 inhibitor, and a fixed-ratio injectable combination of a GLP-1 receptor agonist with insulin. Pre-mixed insulins are identified with the proportion of the shorter-acting component first in Europe but second in the USA. Abasaglar is a biosimilar glargine. Prescribers are encouraged to check national and local formulary directives. ^ Based on ADA/EASD consensus statements.

Table 2. The pre-insulin era dating from 1869 (when Paul Langerhans described the pancreatic islets) to 1922 (successful clinical application of a pancreatic extract in Toronto). The pre-insulin era charts a series of observations and experimental studies linking diabetes with the pancreas, and providing evidence that pancreas extracts can reduce blood glucose and glucosuria in diabetic states.

1869	Paul Langerhans	Description of pancreatic islands
1870	Apollinaire Bouchardat	Reduced glucosuria of diabetes patients during Siege of Paris
1875	Nikolaus Friedreich	Occurrence of diabetes with pancreatic disorders
1884	Louis Vaillard & Charles Arnozan	Pancreatic duct ligation in rabbits caused pancreatic atrophy without hyperglycaemia
1889	Oskar Minkowski & Josef von Mering	Pancreatectomy in dogs caused diabetes, and Minkowski later showed partial reversal of the diabetes by pancreas autotransplantation
1892	Andrea Capparelli	Pancreas extract injected into abdominal cavity of a dog
1893	Gustave Édouard Laguesse	Suggested islands of Langerhans might make an internal secretion that prevents glucosuria
1894	Patrick Watson-Williams	Subcutaneous implantation of sheep pancreas pieces into a severely ill 15-year-old boy with diabetes, who died several days later
1900	Eugene Gley	Pancreas extract injected into pancreatectomized dogs reduced glucosuria (described islet extract in a sealed document which he deposited with the Société Francaise de Biologie in 1905, not opened until 1922)
1901	Eugene Opie	Noted degeneration of pancreatic islets in a diabetes patient and suggested islets might produce an antidiabetic principle
1906	Wilhelm Heiberg	Described method to count islets of Langerhans and noted fewer islets in pancreatic tissue of diabetes patients
1907	John Rennie & Thomas Fraser	Extracts of fish islets consumed and/or injected subcutaneously into 5 diabetes patients sometimes reduced glucosuria
1908	Georg Zuelzer	Pancreas extract (Acomatol) was tested in a patient who died when extract supply ran out. Injections of other extracts in further patients were only temporarily effective
1909	Jean De Meyer	Named putative internal islet secretion 'insuline'. In 1916 Edward Sharpey–Schäfer independently named the secretion 'insulin'
1910	Joseph Pratt	Review of evidence indicating that diabetes is usually associated with lesions of the pancreatic islets: review notes negative and contradictory accounts in the literature
1911	Ernest Scott	Injection of pancreatic extract reduced glucosuria and increased survival of pancreatectomized dogs
1913	John Murlin & Benjamin Kramer	Intravenous injection of pancreatic extracts temporarily reduced glucosuria of pancreatectomized dogs
1919	Israel Kleiner	Intravenous injection of pancreatic extracts reduced blood sugar of pancreatectomized dogs
1920	Moses Barron	Published account of pancreatic lithiasis and changes in pancreatic islets in cases of diabetes: this paper encouraged Frederick Banting to consider pancreatic duct ligation in initial experiments to eliminate pancreatic exocrine tissue
1921	Nicolae Paulesco	Reported work conducted in 1916 showing intravenous injection of pancreas extracts improved the condition of pancreatectomized dogs
1921	Frederick Banting & Charles Best	Intravenous and subcutaneous injection of pancreatic extracts reduced blood sugar of pancreatectomized dogs: some survived >3 months
1922	Banting and colleagues	Improve pancreatic extract and administer by subcutaneous injection to Leonard Thomson (13 years old in diabetic coma) on 11 January 1922

Figure 1. Timeline showing the introduction of different classes of glucose-lowering agents. The red line indicates the estimated global prevalence of people with diabetes (in millions), >90% of whom are believed to have T2DM



DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; TZD, thiazolidinedione; 1º, first; 2º, second.

the ideal treatment for all presentations of diabetes and signalled the need for other therapeutic agents (figure 1), particularly to treat people with maturity-onset diabetes.

Metformin

Amongst oral glucose-lowering agents, metformin probably has the oldest lineage. It stems from the use of Galega officinalis (Goat's rue, French lilac) to treat thirst and frequent urination (reference to diabetes?) since the 1700s.[12] Galega was found to be rich in guanidine, shown by Watanabe in 1918 to lower blood glucose in animals. Several derivatives were synthesized in the 1920s, and some were used as treatments for diabetes, but they were gradually discarded as insulin became more widely available.[13] Metformin (dimethyl biguanide) was first synthesised in 1922 in Dublin by Emil Werner and James Bell, and in 1929 two laboratories in Breslau reported that it lowered blood glucose in non-diabetic animals (Hesse and Taubmann; and Slotta and Tschesche).[14-16] Although side effects were minimal, its potency was deemed insufficient for clinical consideration.

Meanwhile, guanidine-based antimalarial agents such as proguanil were developed in the mid-1940s and reported to lower blood glucose in animals, and metformin was tested for antimalarial activity by Eusebio Garcia in the Philippines in 1949. Garcia noted that metformin was helpful in treating a local influenza outbreak, and metformin became used for a time as an anti-influenza agent (flumamine).[17] Lowering of glucose was noted in some patients, but again this property was not taken further.

The trail now jumps to Paris where, in 1956, pharmaceutical laboratory owner Jan Aron recruited local physician Jean Sterne to re-assess the glucose-lowering properties of biguanides.[18] Sterne must have been familiar with the field as he had assisted in a study of a guanidine derivative (galegine) as an intern. At Aron Laboratories Sterne worked in collaboration with pharmacist Denise Duval to examine the effects of several guanidine-based compounds (including metformin and phenformin) in animal models. Unknowingly they repeated studies from the 1920s, and were attracted by the effectiveness and tolerability of metformin. Reassured by accounts of flumamine use in humans, Sterne ventured to test metformin in the diabetes clinic and published a first account of this work in a Moroccan medical journal in 1957.[19] To expand the clinical studies, Sterne co-opted colleagues in local hospitals and noted that metformin could reduce or replace the need for insulin in some individuals with maturity-onset diabetes, but could not eliminate the need for insulin in young individuals with diabetes.[18]

Metformin was introduced in Europe as a treatment for maturity-onset diabetes in 1958, and other biguanides were introduced at about the same time (phenformin widely: buformin in parts of Europe but not the UK). These other biguanides initially received preference over metformin due to their greater glucose-lowering efficacy, but were withdrawn in the late 1970s due to an unacceptably high occurrence of lactic acidosis.[20] The therapeutic advantages of metformin were confirmed by extensive studies in Edinburgh in the 1960s and by the United Kingdom Prospective Diabetes Study which reported in 1998. However, it was not until 1995 that metformin was introduced into the USA, and several years later metformin replaced sulphonylureas as the primary oral glucose-lowering therapy for T2DM.[20,21]

Sulphonylureas

Sulphonylureas were discovered as a side effect of sulphonamide antibacterial drugs, which were known since the 1930s to sometimes lower blood glucose. In 1942 in Montpellier (France) Marcel Janbon observed particularly severe hypoglycaemia causing convulsions and coma in some patients with typhoid and pneumonia

whom he treated with the sulphonamide 2254RP (1-butyl-3-sulfonylurea), later termed carbutamide.[22] Local physiologist, August Loubatières confirmed the hypoglycaemic effect in animal studies and by 1946 he provided evidence for a direct action on the pancreas to stimulate insulin secretion. Loubatières considered the therapeutic potential of the agent to treat diabetes, but this was not taken further.[23] Indeed, the hypoglycaemia was regarded as a side effect that limited continued use of carbutamide for antibacterial purposes, and use of carbutamide was mostly confined to East Germany and eventually discontinued.[24]

Under the name BZ55, carbutamide was re-investigated by Boehringer Mannheim, with studies at a Berlin hospital by Hans Franke and Karl Fuchs in 1954.[25] Franke and Fuchs were not aware of the 'hypo' history of the drug but quickly noted this side effect. Indeed, Fuchs tested the drug on himself, noted the potency of the hypoglycaemic effect, and conducted tests in people with diabetes, observing most effect in those with adult-onset diabetes. A race to market a treatment for adult-onset diabetes began with carbutamide in 1955, followed by several closely related (now called first-generation) compounds (tolbutamide, chlorpropamide, tolazamide and acetohexamide). However, controversy over long-term safety resulted in all but tolbutamide being discontinued over the next five decades, and equivocal findings of the University Group Diabetes Program (UGDP) trial brought into question the cardiovascular (CV) safety of tolbutamide.

In the 1970s and 1980s the first-generation agents were superseded by agents designed to give higher potency (glibenclamide, glipizide, gliclazide) and there was a further addition (glimepiride) in the 1990s.[26,27] Although much was known about the insulin secretory dynamics afforded by sulphonylureas, it was not until the late 1980s that the cellular mechanism of action was determined, namely binding to the so-called sulphonylurea receptor (SUR1) and closure of the inwardly rectifying K^+-ATP channel (Kir6.2).[28] Sulphonylureas remained the main oral glucose-lowering therapy for T2DM until around the turn of the 21st century when they were superseded by metformin, reflecting the weight gain with sulphonylurea therapy and the risk of hypoglycaemia consequent to continued stimulation of insulin secretion at low glucose levels.[27]

Meglitinides

Although there had been reports of benzoic acid derivatives lowering blood glucose, it was particularly the work of Jean-Claude Henquin and his group in Louvain in the late 1970s that gave rise to the meglitinide class.[29,30] They noted that the non-sulphonylurea benzamido moiety of glibenclamide (meglitinide; HB 699) could stimulate insulin secretion similarly to sulphonylureas, indicating what is now recognized as a separate binding site on SUR1. Based on the meglitinide molecule, repaglinide was designed by the Karl Thomae company to increase binding affinity, and (though not so closely related) nateglinide was designed by Ajinomoto. These agents were introduced in the late 1990s and the turn of the millennium, respectively, to serve as 'prandial' insulin releasers with a faster onset and shorter duration of action than sulphonylureas.[31] Their use, however, was limited and declined in parallel with sulphonylureas.

Alpha-glucosidase inhibitors

As part of a screening programme for amylase inhibitors at Bayer in the 1970s, acarbose was isolated from cultures of a strain of Actinoplanes bacteria and found to be a potent competitive inhibitor of intestinal glucosidases.[32,33] Acarbose was introduced in 1990, and two other alpha-glucosidase inhibitors (miglitol and voglibose) were introduced in some regions in the mid-1990s: these were synthesised, based on the discovery of sugar derivatives isolated from strains of Bacillus and Streptomyces.[33] Though helpful in reducing the prandial glucose excursions from carbohydrate-rich meals, and gaining considerable use in some Asian countries, alpha-glucosidase inhibitors received little use in western countries due to their modest overall efficacy and gastrointestinal side effects.

Thiazolidinediones

The discovery of thiazolidinedione (TZD) peroxisome proliferator-activated receptor (PPAR) gamma agonists preceded the identification of PPAR transcription factors (circa 1990). While in search of clofibrate analogues with additional triglyceride-lowering activity, Takeda Chemical Industries in Japan observed in the late 1970s that some compounds (particularly thiazolidine derivatives) had glucose-lowering activity in insulin-resistant and diabetic mice. One such compound, ciglitazone, was evaluated in detail but was not considered potent enough to develop as a glucose- and lipid-lowering drug.[34] However, the molecular template gave rise to pioglitazone, which was marketed in 1999.[35] Other thiazolidine derivatives were developed by design, notably troglitazone by Sankyo in 1988 (with Warner Lambert), which became the first TZD to be approved for clinical use in the United States in 1997. It was withdrawn in 2000, however, due to idiosyncratic liver toxicity. Also using a thiazolidine structure, SmithKline Beecham (later GlaxoSmithKline) synthesized rosiglitazone in 1988 and brought it to market in 1999.[35]

Following a meta-analysis (2007) that raised cardiovascular (CV) safety concerns, rosiglitazone was withdrawn in Europe in 2010 and restricted in use in the USA.[36] However, a large CV outcome study (RECORD) did not confirm the concerns; restrictions in the USA were lifted in 2013, although rosiglitazone has since received little use. Studies with pioglitazone have suggested possible reductions in myocardial infarction and stroke, but the increased risk of heart failure has limited prescriber uptake. Questions regarding bladder safety, although unconfirmed, have excluded use of pioglitazone in some countries.[37]

Incretin analogues

Since the discovery of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP, 1970s) and glucagon-like peptide-1 (GLP-1, 1980s), the abilities of these hormones to enhance nutrient-induced insulin secretion have been viewed with interest as potential therapies for T2DM. Attention became focused on GLP-1 because (unlike GIP) it also reduced glucagon secretion and maintained greater insulin-releasing efficacy in people with T2DM as well as exerting a satiety effect and reducing body weight.[38,39] However, rapid degradation by the enzyme

dipeptidyl peptidase-4 (DPP4) precluded therapeutic use of GLP-1 itself.[40]

In 1992, when John Eng (New York) was investigating pancreatitis caused by reptile venoms he discovered the peptide exendin-4 in the venom of the Gila monster (Heloderma suspectum), and recognized this as having considerable (53%) sequence homology with GLP-1.[41,42] Despite its ability to mimic the effects of native GLP-1 and resist rapid degradation by DPP4 (due to a glycine residue at N2), it was several years before a company (Amylin Pharmaceuticals) acquired the rights and formulated the molecule into an injection - exenatide - which was introduced in 2005 as a treatment for T2DM. Later, encapsulation of exenatide within polylactide-co-glycolic acid microspheres enabled once-weekly injection. Further members of the GLP-1 receptor agonist class have been based on either the exendin molecule (lixisenatide) or aligned more closely with native GLP-1 (liraglutide, dulaglutide, semaglutide) with modifications at residue N2 to avoid rapid breakdown by DPP4.[43] Also, linkage to an immunoglobulin (dulaglutide) or inclusion of a fatty acid chain to enable attachment to albumin (liraglutide, semaglutide) have been used to extend time within the circulation. During their use in the treatment of T2DM and obesity, members of the GLP-1 receptor agonist class have shown reductions of blood pressure and in some CV complications as well as decreased albuminuria. Additionally, members of the class are under investigation for the treatment of fatty liver, dementia and low bone density.

With advances in custom peptide production, attention has been given to the design of single peptides that can interact with multiple receptors to achieve a greater lowering of blood glucose and body weight than can be achieved with existing GLP-1 analogues. The first so designed peptide to be approved (tirzepatide, 2022) to treat T2DM is a dual incretin agonist activating receptors for GLP-1 and GIP.[44] The highest dose of tirzepatide tested (up to 15 mg once weekly over 40 weeks) in people with T2DM achieved reductions in HbA_{1c} by >2% (>22 mmol/mol) and body weight by >9 kg. In obese people without diabetes the 15 mg once-weekly dose for 72 weeks achieved weight loss of 20%.

DPP4 inhibitors

The DPP4 inhibitors provide us with an example of glucose-lowering drugs obtained entirely by design. Given the susceptibility of incretin hormones to rapid inactivation by DPP4, it was appreciated that inhibitors of the peptidase activity offered a therapeutic strategy to enhance the endogenous incretin effect via both GLP-1 and GIP concentrations.[40,45] Encouraged by reports in the early-mid 1990s that DPP4 could be inhibited using various pyrrolidines and thiazolidines, Edwin Villhauer at Novartis in New Jersey screened a wide range of inhibitors to construct a topographical profile of the peptidase catalytic site. From this he designed vildagliptin (1998; the 'vilda' recognises his work) to block the site by reversible covalent bonding.[46] Regulatory approval of vildagliptin (2007) was delayed to acquire additional phase 3 safety data, allowing a fast and effective development programme to bring sitagliptin to market (2006) to become the first in class.

The design of sitagliptin involved molecular modelling of the peptidase site using X-ray crystallography imaging. This enabled Nancy Thornberry and Ann Weber at Merck (MSD) in the USA to evaluate the ability of a series of piperazine derivatives to block the site non-covalently.[47] Other DPP4 inhibitors are either covalent inhibitors (e.g. saxagliptin) or non-covalent inhibitors (e.g. linagliptin, alogliptin). Most of these agents are given as once daily (vildagliptin is given twice daily) tablets, but very long-acting (once-weekly, e.g. omarigliptin) DPP4 inhibitors are available in some regions. DPP4 inhibitors gained a reputation for their safety profile (which has been generally neutral in CV outcome studies) and have replaced TZDs as add-on therapy to metformin.

SGLT2 inhibitors

The isolation of salicylic acid from willow tree bark in the 1820s stimulated chemists to investigate other trees for compounds of potential medicinal interest. In 1835 the professor of chemistry at Louvain (Jean-Baptiste Van Mons) was moving his apple tree nursery. Two of his assistants, Laurent-Guillaume de Koninck and Jean Stas, identified phlorizin in root bark from the trees.[48,49] Although phlorizin didn't show any obvious medicinal value, in 1886 Josef von Mering (Strasbourg) described its blood glucose-lowering and renally-induced glucosuric effects. However, the glucosuria became viewed as indicative of a form of diabetes and although many groups investigated the effects of phlorizin it was not assigned a medicinal use.[50]

In the late 1950s Robert Crane in Saint Louis added the intestine to the sites of action of phlorizin when he used it as an inhibitor of intestinal sodium-dependent glucose transport.[51] However, it was not until the mid-1980s that studies at Yale by Ralph DeFronzo, Gerry Shulman, Luciano Rossetti and colleagues showed that phlorizin could reduce the hyperglycaemia of partially pancreatectomised diabetic rats.[52] This attracted a rethink of the potential medical value of phlorizin but its low solubility and low potency hampered development. Several O-glycoside derivatives of phlorizin (e.g. Tanabe T-1095 and Kissei's remogliflozin) showed improved activity, but it was William Washburn and colleagues at Bristol Myers Squibb in 2000 who determined that C-glycoside derivatives avoided hydrolysis by intestinal glucosidases and thereby increased bioavailability.[53] With further molecular manipulation the selective SGLT2 inhibitor dapagliflozin was produced (approved in Europe 2012) and other C-glycoside derivatives were produced with varying degrees of selectivity for SGLT2 inhibition (e.g. canagliflozin, approved in the USA in 2013, followed by empagliflozin and ertugliflozin).[54] The cardio-renal effects of these agents, notably to reduce blood pressure and to reduce risk and progression of heart failure and chronic kidney disease independent of glycaemic control, have generated indications beyond the management of diabetes.[55]

Evolving fashions in diabetes management

The emergence of each class of glucose-lowering agents has created a succession of 'fashions' in the therapeutic management of hyperglycaemia, especially for T2DM. For example, sulpho-

Table 3. Origins of non-insulin glucose-lowering agents.

Class and first agent	Origin by discovery or design
Sulphonylurea *Carbutamide 1955*	Sulphonamide antibacterial drugs cause hypoglycaemia (1930s – 1940s), especially carbutamide, discontinued as antibacterial. Carbutamide re-investigated by Boehringer Mannheim in early 1950s, hypoglycaemic effect studied in diabetes patients by Hans Franke and Karl Fuchs (1954).
Biguanide *Metformin 1957*	Herbal use of Galega officinalis (since 1700s), rich in guanidine which has glucose-lowering property (1918). Metformin synthesized 1922, shown to lower glucose (1929), forgotten, re-discovered as antimalarial and anti-influenza agent (1940s), re-studied for treatment of diabetes by Jean Sterne at Aron Laboratories (1956-7).
Alpha-glucosidase inhibitor *Acarbose 1990*	Identified during screening programme for amylase inhibitors by Bayer in 1970s
Thiazolidinedione *Troglitazone 1997*	Ciglitazone (not developed) identified during screening for triglyceride-lowering fibrates by Takeda in the late 1970s.
Meglitinide *Repaglinide 1997*	Insulin-releasing property of benzamido part of glibenclamide (meglitinide) noted in late 1970s. Repaglinide developed by Karl Thomae Company (later Boehringer Ingelheim and licensed to Novo Nordisk).
GLP-1 receptor agonist *Exenatide 2005*	Exendin-4 identified in the saliva of the Gila monster lizard (Heloderma suspectum), and marketed as exenatide by Amylin Pharmaceuticals.
DPP4 inhibitor *Sitagliptin 2006*	DPP4 found in 1990s to inactivate incretins, and peptidase site blocked by pyrrolidines and thiazolidines. Vildagliptin designed by Edwin Villhauer at Novartis (approved 2007) and sitagliptin designed by Nancy Thornberry and Ann Weber at Merck (MSD, USA) - developed faster (marketed 2006).
SGLT2 inhibitor *Dapagliflozin 2012*	Phlorizin isolated from apple tree root bark (1835), noted glucosuric (1886) and antidiabetic (1987): modified to prevent intestinal degradation and selectively inhibit SGLT2 by William Washburn at Bristol Myers Squibb (2000) to produce dapagliflozin.

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2

nylureas and meglitinides generated focus on beta cell dysfunction, which was the main target for glycaemic management of T2DM up to the early 1990s. Acarbose generated focus on prandial glucose excursions and their link to cardiovascular risk, before attention shifted to insulin resistance with the rise of metformin and thiazolidinediones - each of the latter three classes emphasizing the avoidance of hypoglycaemia. The DPP4 inhibitors facilitated straightforward combination therapy with metformin, while the weight-lowering properties and cardiorenal benefits of GLP-1RAs and SGLT2 inhibitors have moved CV and renal considerations to the fore in the most recent treatment guidelines.[56]

Dietary fashions, too numerous to elaborate here, have featured alongside drug-related fashions in the management of diabetes and cardiovascular risk. Interestingly, before insulin was discovered, type 1 diabetes and unspecified type 2 diabetes were treated with starvation diets: a hundred years later the low-calorie approach is again favoured for type 2 diabetes.[57]

Conclusion

Most non-insulin glucose-lowering agents (DPP4 inhibitors excepted) have arisen from chance clinical or scientific observations that were followed up with extensive experimental refinements (Table 3). Nearly all have incurred a long 'adoption time' from initial circumstantial evidence to therapeutic purposing, but once a lead agent is established there is invariably a race to design 'look-alike' compounds. All drug classes have experienced early safety scares and most have shown that effective clinical advantage can be gained before there is a full understanding of the mechanisms, provided the implementation of safe prescribing practice is respected.

Key messages

- Most non-insulin glucose-lowering agents arose from chance clinical or scientific observations.
- When a new class of glucose-lowering agent is developed, 'look-alike' agents quickly follow.
- Effective clinical use of an agent can proceed without detailed mechanistic understanding, provided it can be prescribed safely.

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