



Review Article

Concise review on anti-diabetic agents: Traditional to modern

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ARTICLE INFO

Article history:

Received 06-09-2023

Accepted 18-10-2023

Available online 06-11-2023

Keywords:

Diabetes

Antidiabetic agents

Hypoglycemic agents

Insulin

Sulfonylureas

ABSTRACT

Diabetes is one of the major challenging diseases as it is associated with other health complications including Atherosclerosis (narrowing of blood vessels), Heart diseases, Neuropathy (nerve damage in limbs), and Hypertension (high blood pressure). Its prevalence has been precarious since the last decade. Researchers have been trying hard to find the best remedy for diabetes since the last century and have developed a whole range of drugs of various chemical classes to control the mortality rate. Antidiabetic drugs synthesized during the last century are classified into three stages in the present review article and certain examples with their structure, mode of action, and applications are briefly discussed in the article. The future aspect, drug of choice, and success rate have been discussed as well.

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1. Introduction

Diabetes mellitus comprises of a Greek word 'diabetes', i.e., to go through, and a Latin word 'mellitus', i.e., sweet. In 150 AD Arateus, a Greek physician of Cappadocia was the first one to use the word diabetes. WHO (World Health Organization) defines diabetes as, a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. It is also known as Hyperglycaemia or Adult-onset diabetes.¹

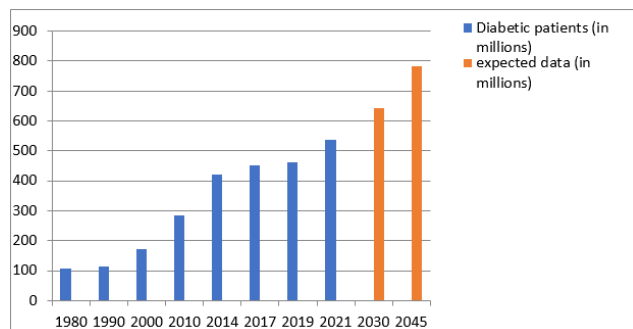
ADA (American Diabetes Association) classifies diabetes into 4 categories, namely, Type 1 diabetes or IDDM (Insulin Dependent Diabetes Mellitus), Type 2 diabetes or NIDDM (Non-Insulin Dependent Diabetes Mellitus), specific types of diabetes due to other causes, and gestational diabetes mellitus. The causes of type 1 and Type 2 diabetes are destruction of β -cells and loss of adequate insulin secretion by β -cells respectively. The cause of diabetes of a specific type includes exocrine

pancreas disease, chemically induced diabetes, monogenic syndromes, etc. Gestational diabetes refers to the diabetes diagnosed during pregnancy usually second or third trimester.² Diabetes caused in childhood is usually type 1 diabetes and if caused in later stages is likely to be Type 2. The cause of IDDM is the sum of complex genetics, immune factors, and environmental factors. However, family history, obesity, and diet govern Type-2 diabetes.³

Constant hunger, frequent thirst, often urination, extreme weight loss, fatigue, blurred vision, dry skin, slow-healing wounds, and high glucose levels in the blood are some obvious symptoms of type-2 Diabetes Mellitus. Risk factor of type-1 diabetes includes younger age and genealogy while in type-2 diabetes; obesity, lifestyle, old age, low physical activity, and gestational prediabetes. If diabetes is not treated on time, it can damage blood vessels, nerves (neuropathy), kidneys, and eyes. It also leads to chronic conditions like gastroparesis and sometimes leads to coma. Diabetes cannot be cured completely however it can be controlled with hypoglycemic agents that are classified in Table 1.

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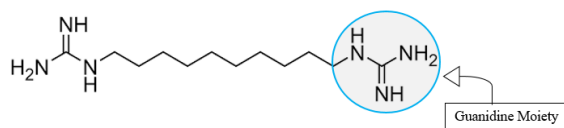
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Graph 1: Number of diabetic patients globally

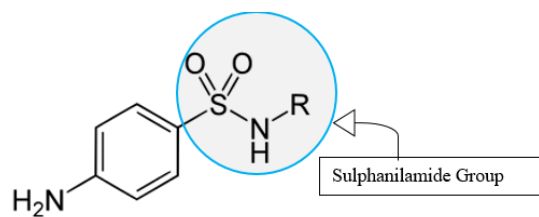
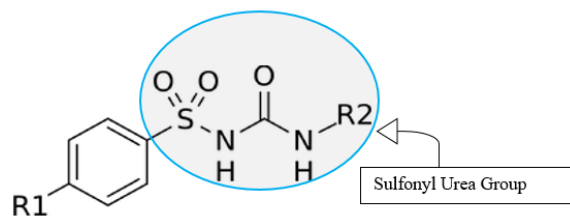
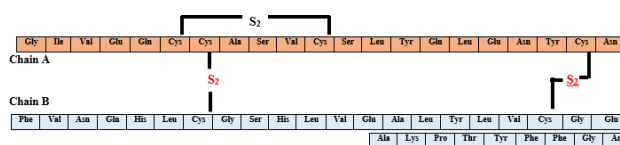
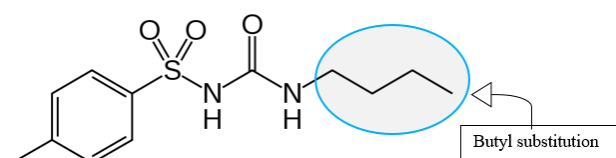
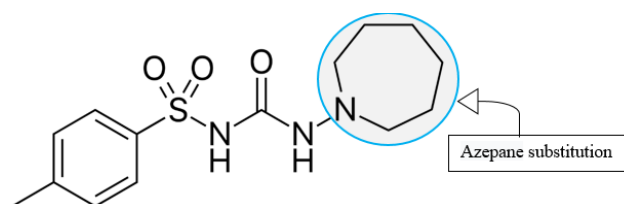
Table 1: Classification of antidiabetic drug

Antidiabetic Class	Examples
Sulfonylureas:	Tolbutamide, Glimperide
SGLT-2 Inhibitors:	Dapagliflozin, Ertugliflozin
Thiazolidinediones:	Pioglitazone, Rosiglitazone
Meglitinides:	Nateglinide, Repaglinide
α -Glucosidase Inhibitors:	Acarbose, Miglitol
DPP-4 Inhibitors:	Alogliptin, Sitagliptin
Amylin Analogues:	Pramlintide
Biguanides:	Metformin, Phenformin
GLP-1 Agonists:	Albiglutide, semaglutide
Insulins:	<i>Short Acting:</i> Regular Insulin <i>Intermediate Acting:</i> Insulin Isophane <i>Long Acting:</i> Insulin Glargine <i>Combination Insulins:</i> Insulin Aspart Insulin Lispro Insulin Detemir

**Fig. 2:** Structure of synthaline(1920)

Patients also need to check their blood glucose level regularly, alter their lifestyle accordingly, have some physical exercise, eat healthy natural food, control their weight, and follow medications through doctor's guidance.

Cases of patients suffering from diabetes have increased from 10,800,000 in year 1980[WHO] to 53,700,000 in 2021. International Diabetes Federation (IDF) expects the rise of diabetic patients to 64,300,000 by 2030 and 78,300,000 by 2045. 90% of the patients suffering from diabetes are NIDDM patients. The disease is more prevalent in the age

**Fig. 3:** Structure of sulphanilamide (1930)**Fig. 4:** Structure of sulfonyl urea (1937)**Fig. 5:** Structure of insulin**Fig. 6:** Structure of tolbutamide (1950)/Carbutamide if NH₂ at Para position (1956)**Fig. 7:** Structure of Tolazamide

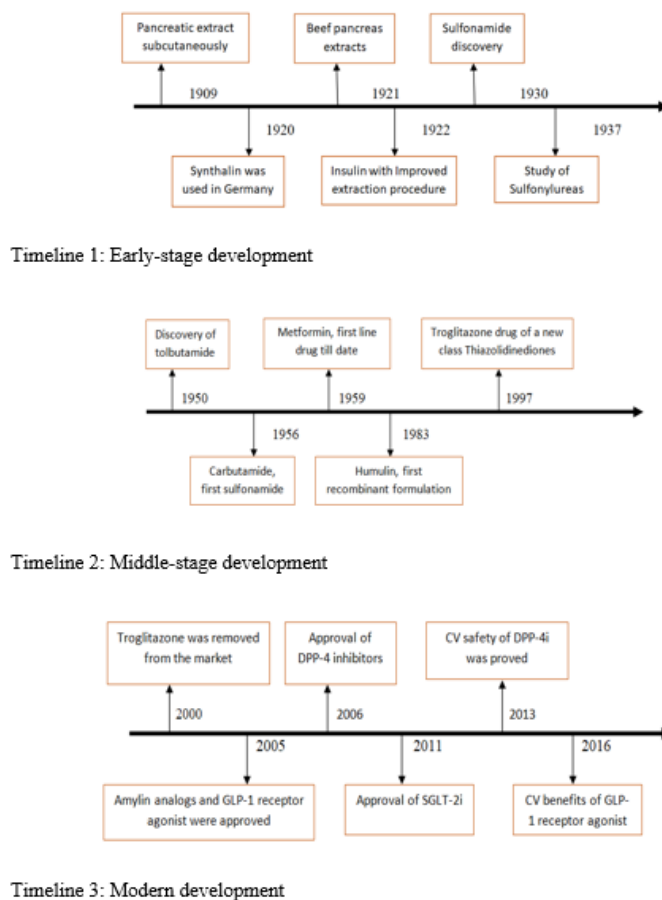


Fig. 1:

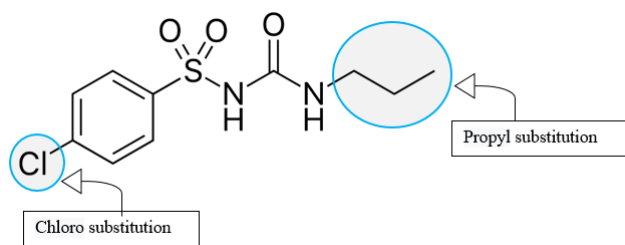


Fig. 8: Structure of Chlorpropamide

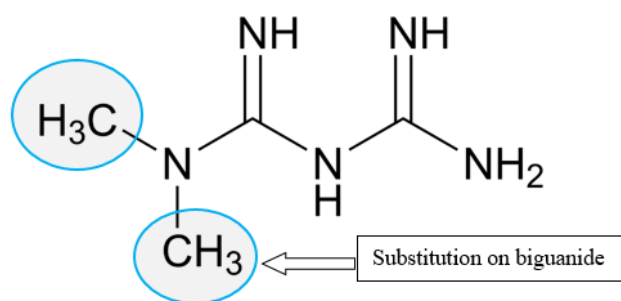


Fig. 9: Structure of metformin (1959)

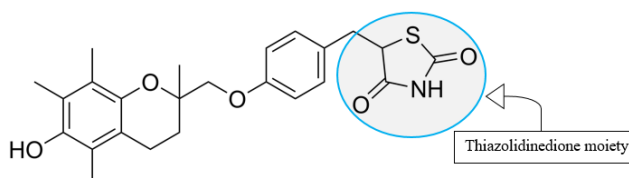


Fig. 10: Structure of troglitazone (1997)

group above 50 as compared to the age of 20-24. Discussing gender distribution, men are more prevalent as compared to women. Also, the number of patients living in the urban areas is more than that of the rural areas.⁴ According to a recent study by ICMR (Indian Council of Medical Research–India Diabetes (ICMR-INDIAB), India has over 10 crore diabetic patients in 2023 which has increased at a rate of 10 percent annually within the last four years. The study adds that more than 13 crore Indians are prediabetic. Two states Goa and Kerala have the highest number of diabetic patients in the country.⁵ The risk of diabetes is also

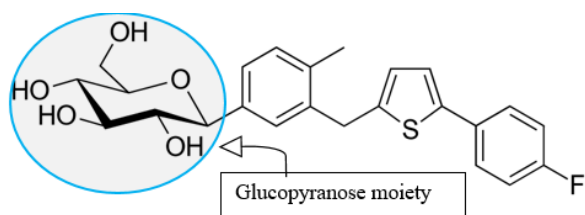


Fig. 11: Structure of Canagliflozin (2013)

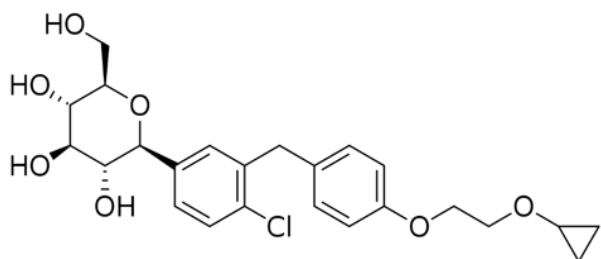


Fig. 12: Structure of Bexagliflozin (2023)

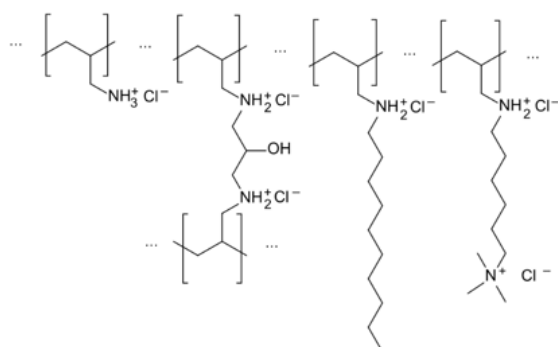


Fig. 13: Structure of Colesevelam (2008)

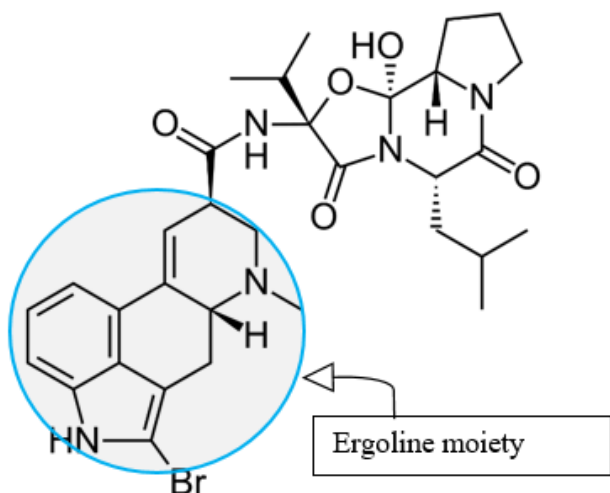


Fig. 14: Structure of Bromocriptine (1975)

expanding globally. Graph 1 represents the situation in the past, present, and future of diabetes.

2. Discussion

2.1. Early-stage development of anti-diabetic drugs: [1900-1950]

Before World War 1, Goerge Zuezler 1909 injected pancreatic extract into 8 patients in Berlin subcutaneously. Synthalin, a guanidine compound, was used to treat diabetes in Germany during the 1920s by Frank et al. In 1921 December Banting and Charles Best, his student added beef pancreas extracts and alcohol which were later washed with toluene a couple of times and then filter sterilized. The test solution then termed 'insulin' was all set for its 1st clinical trial. Leonard Thompson, aged 14 weight 30 kgs was injected with this insulin in 1922 on the 11th of January. The results observed were a slight fall in glucose blood level and sterile abscess. Collip, a skilled chemist, who joined Banting in late 1921 improved insulin's quality and extraction procedure. Thompson was again injected with improved insulin on 23rd January. The results turned out to be excellent followed by the disappearance of urinary ketose. Insulin was widely made available to Europe and North America by the month of October in the year 1923. Another major advancement was the crystallization of insulin in the year 1926. The first long-acting insulin was PZI (protamine-zinc insulin) which was commercially made available in 1936. The second long-acting insulin was released in 1946, namely, NPH (Neutral protamine Hagedorn) which contained crystals of zinc insulin along with protamine (10%) of PZI. PZI was not as short-acting as NPH which was open for combination with normal insulin.

Sulphonamides' hypoglycemic effect was determined in 1930. The capability of the Sulphonamide group to show hypoglycemic effect was experimentally demonstrated by 1946 but the work was left a bit unnoticed for about 10 years. The study of sulfonylureas, abbreviated as SU, in producing hypoglycemic effects started in 1937. After about 5 years, Marcel Janbon along with his colleagues observed hypoglycemia due to sulfonamide-derived antibiotics while treatment of typhoid. The ability of aryl sulfonylureas to stimulate insulin release was confirmed in 1946.⁶⁻⁹ Timeline 1 represents the consecutive development of hypoglycemic agents during the early stage.

1. **Synthaline:** Synthaline was the first Anti-diabetic drug identified with the molecular formula $C_{12}H_{28}N_6$. It is a guanidine base compound which is an aminocarboxamide group. Synthaline has a long chain consisting of ten carbons and it shows an identical effect to insulin. The guanidine structure increases ionic interactions with the receptor. Its chemical name is 1,10-diguanidodecane. The structural formula of Synthaline is shown in Figure 1.

Synthaline was found to be hepatotoxic,¹⁰ so later it was removed from the market. Later on, another synthaline molecule with 12 carbon chain was developed and named Synthaline B.

2. **Sulphonamide:** Sulphonamide is a structure possessing a sulphanilamide functional group upon the benzene ring and amino group at the para position. The structure is shown in Figure 2. It has a structure similar to Para Amino Benzoic Acid. Attaching different groups at R of sulphonamide gives rise to many important drugs. Thiazides (diuretic), sulfonylurea (hypoglycemic), and acetazolamide (glaucoma) are similar examples containing the sulphonamide group. Sulphonamides are also known as sulpha drugs. Initially, sulphonamides were used as antibacterial agents later their therapeutic effects were expanded. Para amino group is essential for activity. Neither the amino group nor its position can be changed otherwise therapeutic effect might be lost. An aliphatic ring or chain instead of a benzene ring will lose activity. The Sulphanilamide group must be directly attached to the aromatic ring. The beta cell has been desensitized by sulfonamides.¹¹
3. **Sulfonyl Urea:** Sulfonylurea is a significant class of antidiabetic drugs derived from sulphonamide. It has a carbamide group attached to SO₂. The structure is shown in Figure 3. It is widely used in type-2 diabetes mellitus. They increase the secretion of insulin from beta cells.¹² Substitutions such as halogens, small alkyls, aryls, etc. at the R1 improve antidiabetic activity. The R2 portion, adjacent to terminal nitrogen, should be substituted with a 3 to 12-carbon chain to create a more lipophilic structure. Glipizide, Glibenclamide, Glibornuride, Gliclazide, Glycropyramide, Glimepiride, Glipizide, Gliquidone, Glisoxepide, Tolazamide, Tolbutamide are antidiabetic drugs containing sulfonyl urea structure.
4. **Insulin:** Insulin is a polypeptide pancreatic hormone consisting of 51 amino acids divided into two major chains. Chain A has 21 and chain B has 30 amino acids. Both chains are interlinked via disulfide bonds as shown in Figure 4. Its molecular formula is C₂₅₇H₃₈₃N₆₅O₇₇S₆ and its molecular weight is 5808 g per mole. Insulin regulates blood glucose levels. Disulfide linkage is essential for insulin's activity, breaking this bond inactivates the hormone. Scientists have developed many insulin analogs for better ADME. They act similarly to insulin. Lispro, Aspart, Guilisine, Degludec, and NPH (Neutral Protamine Hagedorn) are some examples of insulin alternatives that can be utilized in diabetes mellitus.¹³

2.2. Middle-stage development of anti-diabetic drugs: [1950-2000]

Tolbutamide, the first sulfonylurea, was marketed during the 1950s in Germany. The tolbutamide was followed by Tolazamide, Chlorpropamide, and Acetohexamide categorized as first-generation sulfonylureas.⁹ In Berlin, Frank and Fuchs rediscovered sulfonamides in 1956 resulting in the development of the Tolbutamide compound and carbutamide followed by other compounds like Tolazamide in the upcoming decade along with Chlorpromide.⁸ The series lens of insulin was formulated in 1956 which comprised of lente, followed by semilente, and then finally ultralente. The composition of lente was 7 parts of ultralente with 3 parts of semilente and showed intermediate action. On the other hand, semilente and ultralente were found to be slow and long-acting respectively.¹⁴

Metformin, the only biguanide being used, was discovered in the year 1959 but its approval in the US was made in the 1990s. 1983 marks the approval of human insulin, the first recombinant formulation. The rapid-acting analog of human insulin, lispro, marks its approval in 1996.⁹ Acarbose, the first α -glucosidase inhibitor was discovered in 1995 followed by the discovery of miglitol in 1996.¹⁵ Also, a new class of antidiabetic agents, Thiazolidinediones or TZD, the first drug being Troglitazone, was approved in the US in 1997. The drug was then discontinued due to its side effect of hepatotoxicity in 1999.¹⁵ Timeline 2 denotes the successive development of antidiabetic drugs during the middle stage.

1. **Tolbutamide:** Tolbutamide, a sulfonylurea, falls under the category of benzene sulphonamides and has a molecular formula C₁₂H₁₈N₂O₃S shown in Figure 5. Tolbutamide stimulates insulin secretion and its utilization resulting in the lowering of blood glucose levels. The methyl group at the para position gets oxidized to the acid group promoting its elimination. Hence, the substitution of the methyl group by the chloro group (Chlorpropamide) makes the drug metabolism resistant and provides a longer duration of action.¹⁶
2. **Carbutamide:** Carbutamide, developed by Servier, was approved in 1956 having molecular formula C₁₁H₁₇N₃O₃S shown in Figure 5. Carbutamide acts by stimulating the secretion of Insulin from β -cells of the Pancreas. Carbutamide has a longer half-life. Carbutamide showed toxic effects on bone marrow and hence was removed from the market. Moreover, its metabolism into nitroso-derivative caused medullary toxicity.¹⁷ Substitution of the Aniline moiety by the toluene, i.e., replacing the -NH₂ group with the CH₃ group resulted in tolbutamide.

3. **Metformin:** Metformin, dimethyl biguanide, having molecular formula $C_4H_{11}N_5$ is the first-line drug for the treatment of Diabetes Type II. The structure is shown in Figure 8. Metformin improves glucose tolerance by lowering the basal as well as postprandial glucose levels in plasma. Moreover, it increases peripheral glucose uptake along with its utilization resulting in improved insulin sensitivity. Other mechanisms associated involve decreased intestinal absorption and hepatic production of glucose.¹⁸ It is a stable crystal structure due to the presence of Hydrogen bonds and forms a hydrophilic cationic base at physiological pH. Metformin is a planar molecule with 2 non-polar methyl groups and protonation between the imino group. The imino groups possess the chelating property.
4. **Thiazolidinediones:** Thiazolidinediones, also known as Glitazones belong to the class of heterocyclic compounds comprising C_3SN , a five-membered ring. Troglitazone, a thiazolidinedione is shown in Figure 9. It regulates the gene expression by binding to the PPAR- γ (Peroxisome proliferator-activated receptor gamma) receptor which regulates energy homeostasis. The genes activated by the PPAR- γ receptor are present in the liver, fat, muscle, adipocyte differentiation, fatty acid storage, and glucose metabolism. PPAR- γ agonists improve the resistance of insulin by increasing GLUT4 (Glucose transporter type 4) expression, increasing adiponectin, and opposing TNF- α (Tumour Necrosis Factor-alpha) effects in adipocytes.¹⁹

2.3. Modern development of anti-diabetic drugs: [2000-2023]

All drugs approved after the year 2000 are categorized under second-generation anti-diabetic drugs.²⁰ In March of the year 2000, the FDA (Food and Drug Administration, US) removed Troglitazone from the market as a result of the death of 63 patients due to hepatic failure. The Thiazolidinediones currently available in the market are Rosiglitazone and Pioglitazone. Rosiglitazone was considered a threat to increased MI (Myocardial infarction) risk and was hence not available before November 2013. However, Pioglitazone is possibly associated with bladder cancer.²¹

Amylin analogs were approved in 2005 by the FDA along with GLP-1 receptor agonists. In the year 2006, DPP-4 (Dipeptidyl Peptidase 4) inhibitors were approved. The incretin-dependent therapies were approved in 2005 and 2006. In the UK, DPP-4 inhibitors were licensed in 2007. SGLT-2i (Sodium Glucose Cotransporter-2) proved cardiovascular safety and was approved in the year 2011. Gliptins were found to be CV-safe in 2013 and were proven for renal safety during 2015-2019. In June 2016,

the CV benefits were proved of GLP-1 (Glucagon-like peptide-1) receptors. The combinations of biguanides were approved in 2004 with SU, in 2005 with TZD, followed by DPP-4i in 2007, and SGLT2i in 2014. Colesevelam, a bile acid sequestrant, and Bromocriptine, a dopamine receptor agonist was approved in 2008 and 2009 respectively. In 2017, Steglatro and Steglujan, SGLT-2i, were approved.^{22–24} Timeline 3 shows the modern development of hypoglycemic drugs.

1. **GLP-1 receptor agonist:** GLP-1 receptor agonist, also known as incretin mimetics, mimics the effects of GLP-1 hormone which is lower in diabetic patients. GLP-1 lowers the sugar level by lowering the hepatic glucose output. The increase in gluconeogenesis reduces the glucagon receptors in the liver which in turn inhibits glucose formation and stimulates glucose uptake. GLP-1 receptor agonists have gained lots of attraction as they effectively lower weight and A1C with a lower risk of hypoglycemia. All GLP-1 receptor agonists are administered subcutaneously except oral semaglutide. The potency and affinity at hGLP-1R were better than GLP-1 itself despite 9 substitutions, namely, Arg36-Lys, and Val33-Ile. Ala30-Glu, Gln23-Lys, Gly22-Glu, Ser18-Glu, Ser17-Thr, Ser14-Asn, and Phe12-Tyr. Asp15, Thr13, Phe12, Gly10, and His7 residues have side chains important for interaction with receptors. Replacement of Ile29 and Phe28 with L-alanine results in reduced receptor activation and affinity.^{25–27}
2. **Amylin analogs:** In the islet of Langerhans, amylin, a 37 amino acid peptide, is secreted along with insulin in a ratio of 1:100 in the case of diabetic patients. Amylin when co-administered with insulin induces a larger reduction in glucagon level and proprandial hyperglycemia as compared to monotherapy of insulin. Amylin assists insulin to control post-meal blood sugar level. Amylin analogues mimic functions of amylin involving inhibition of glucagon release while eating, slowing down emptying time and appetite. The most potential position for fatty acid attachment is the N-terminal part. However, when compared to the S-calcitonin and Pramlintide the attachment of C20-diacid at the N-terminal leads to a loss of potency due to albumin's presence in the assay.^{28,29}
3. **DPP-4 inhibitors:** DPP-4 inhibitors are FDA-approved medications used in the treatment of diabetes and are also referred to as Gliptins. They act on gut hormones, incretin, which carry out glucose homeostasis after food intake. DPP-4 mainly acts on 2 incretin hormones, namely, GLP-1 and GIP (Gastric inhibitory polypeptide) which function to increase the secretion of insulin and decrease the secretion of glucagon respectively. Incretins released after food intake are degraded immediately by DPP-4 because of

their shorter half-life. DPP-4 inhibitors inhibit DPP-4 enzymes resulting in increased GLP-1 and GIP levels which further increases insulin secretion and thereby reduces fasting and postprandial hyperglycemia.³⁰

4. **SGLT Inhibitors:** SGLT-2 inhibitors also known as flozins or gliflozins acting on SGLT-2 proteins are antihyperglycemic medications expressed in PCT (Proximal Convolute tubule). SGLT-2 inhibits the SGLT-2 proteins in PCT reduces reabsorption of glucose, promotes urinary excretion of glucose, and decreases the renal threshold for glucose. Gliflozins contain a glucopyranose structure attached to an aryl ring. The SAR of flozins is not completely understood yet. Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, Sotagliflozin, and Bexagliflozin are SGLT inhibitors approved in the last decade. The structure of Canagliflozin and Bexagliflozin are shown in Figures 10 and 11 respectively. Bexagliflozin is recently approved in 2023.³¹
5. **Colesevelam:** Colesevelam, a bile acid sequestrant, is a synthetic, cross-linked polymer with a cross-linking group and a backbone containing 3 different substituents. The molecular formula of the monomer is $(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl)_2$. Its chemical structure is shown in Figure 12. It is a crosslinked modified polyallylamine structure. Colesevelam's mode of action in reducing the plasma glucose level is not completely known. Researchers, in animal studies, observed an increase in GLP-1 and other incretins due to Colesevelam. Mice models indicated the colesevelam action through TGR5 (Takeda G-protein coupled receptor 5) activation secondary to bile acids binding in the GI tract. The glycogenolysis is suppressed by the activation of GLP-1 and other incretins which may reduce the blood glucose level.³²
6. **Bromocriptine:** Bromocriptine, an ergot alkaloid derivative, with molecular formula $C_{32}H_{40}BrN_5O_5$, is an agonist for dopamine receptors. It is an ergoline analogue. The structure is shown in Figure 13. It is a selective agonist of D_2 receptors and a partial agonist of D_1 receptors. Bromocriptine alters concentrations of monoamine neurotransmitters in the ventromedial and suprachiasmatic nuclei of the hypothalamus which causes a sympatholytic effect resulting in decreased metabolic processes, glucose intolerance, and resistance to insulin.³³

2.4. Drug of choice

Insulin therapy is the only available treatment for patients suffering from diabetes type 1. The combination of rapid and long-acting insulin is preferred injected via syringe and needle. The preferred route of insulin is subcutaneous rather

than intramuscular due to variable results of absorption from IM sites. The drug of choice for diabetes mellitus type 2 is biguanide Metformin. It has been in use for many decades and is the first-line drug. The properties making the drug first line involve its good tolerance, safety, and efficacy along with affordable cost. However, clinical trials have proved lifestyle modifications effective in the prevention or delay of diabetes onset. They have marked a reduction of about 58% in just 3 years.^{34,35}

The ADA suggests SUs, meglitinide, DPP-4i or Pioglitazone to be used if metformin is contraindicated. The IDF suggests SUs, glucosidase inhibitors or meglitinide to be used if metformin is contraindicated.³⁶ Metformin's side effects include Lactic acidosis. They are contraindicated in cases of Renal failure, alcoholism, and severe liver failure. Weight gain and low blood sugar levels are the common side effects of anti-diabetic drugs.^{37,38} Dark urine and upset stomach are major side effects of sulfonylureas. Long-term use of pioglitazone may lead to a damaged liver condition. α -glucosidase inhibitors may induce bloating and GI irritation. The side effects of meglitinides include GI upset, diarrhea, or constipation. DPP-4i may lead to severe joint pain.^{39,40}

3. Future Aspects

Approaches had been aimed to offer a cure to type 1 diabetes via beta cell replacement or supplement. Also, GLP-1 RAs may be effective to unmask beta cells into the immune-affecting cells. Novel approaches include GK (Glucokinase) activators which are responsible for raising insulin threshold secretion. It is also associated with repairing defective islet cells of Langerhans. A new approach to preserve beta cells and enhance their functions has been proposed. Nanocarriers having the ability to improve GI permeation and overcome the stomach's enzymatic degradation are a major area of interest. Studies are aimed at the encapsulation of insulin in chitosan and alginate by calcium chloride through ionotropic pregelation. The in-situ gelation is followed by the alginate-dextran prepared by the nanoemulsion dispersion technique.^{41–43}

The stem cells installation from either an adult source or an embryonic source may result into a potential therapy for diabetes. The transplant of UCMSCs (Umbilical Cord Derived Mesenchymal Stem Cells) may significantly mark improvement in the patient's condition. Han et al., with his colleagues, showed wound healing by mesenchymal stem cells through induction of autophagy. The introduction of the chimeric peptides either dual-action or triple-action may interact with multiple receptors providing better glycemic control. The insulin being injected subcutaneously doesn't mimic insulin release physiologically. Efforts towards this limitation include linking insulin analogs to carriers like graded-sized PEG (Polyethylene glycol). Imeglimin, a tetrahydrotriazene compound, integrated from

metformin may enhance insulin sensitivity, and its secretion from β -cells and prevent fat-induced insulin resistance through hepatic gluconeogenesis suppression.^{44,45} The future aspects in the treatment of diabetes involve microbiome and needle-free insurgency. The transplant of the microbiome from a healthy individual promotes insulin resistance in patients. Needle-free insurgency for monitoring blood sugar/ glucose level like GlucoTrack availability in Europe must be promoted.

4. Success Rate

Deaths due to diabetes increased from 0.61 to 1.37 between 1990 and 2017 i.e., 125.5%. Death rate due to diabetes increased in the middle of the year 2000, and 2019 by 70%. Death due to diabetes in 2019 was 1.5 million, and 3 million in 2021 globally. The increased death rate is believed to be the result of Covid 19. In the US, deaths due to diabetes were reported as 23.1 per million in 1950, followed by 18.1, and 25 in 1980 and 2000 respectively, and lastly 21.6 in the year 2019. In India, deaths due to diabetes rose from 22.30 per million to 27.35 between 1990 and 2019.⁴⁶

5. Conclusion

It is concluded from the above review that diabetes may lead to a pandemic soon if not taken care of. The mortality rate has marked its increment due to the association of the disease with other health conditions and hence broad approaches and wide explorations have become obligatory. The scientific society is trying its best towards the situation. Apart from middle-stage agents and modern-stage agents, efforts are being made toward developing new molecules and therapies to control diabetes. Metal-based drugs, nanocarriers, microbiomes, and recombinant DNA-based supplements are being developed by many pharmaceutical companies and researchers. The pharmaceutical and biotechnological aspects together may provide many better and more advanced combinations with increased compliance and therapeutic action over traditional medication.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Shah JP, Khodakiya AS, Dave NN. Concise review on anti-diabetic agents: Traditional to modern. *Curr Trends Pharm Pharm Chem* 2023;5(4):114-122.