

Metformin Combinatorial Therapy for Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes mellitus (T2D) is a worldwide chronic epidemic with increasing incidence. The current algorithm for medical management of type 2 diabetes includes the pharmacological treatment with nine classes of anti-diabetic drugs. Among the nine classes of drugs approved, metformin, an oral hypoglycemic agent from the biguanide family is widely prescribed as the first-line anti-diabetic monotherapy for the treatment of initially diagnosed T2D individuals. The failure of monotherapy to achieve sustain glycemic control prompted the early use of aggressive combination therapies with other anti-diabetic drugs. The primary aim of T2D treatment is to achieve target glycemic control and reducing further complications of diabetes. Hence, fixed dose combination drugs are preferable in order to reduce pill burden and capital investment. Single pill combinations containing drugs for two different diseases can also be prescribed for avoiding extra medication and to reduce further diabetic complications. Our review addresses the mode of action of anti-diabetic drugs and their combinatorial therapy with metformin.

Keywords: Type 2 Diabetes mellitus; Metformin; Anti-diabetic drugs; Combinatorial therapy; Fixed dose combination drugs

Introduction

Type 2 diabetes mellitus (T2D) is a global public health crisis worldwide, facing escalating epidemic particularly in developing countries. It is one of the most challenging health problems and insidious disease in the 21st century. India is a repository to nearly 62 million diabetics making the world's highest diabetes burden country being termed as the 'diabetes capital of the world'. The number of diabetic patients is set to increase to 69.9 million by the year 2025. India's diabetes numbers are expected to cross the 100 million mark by 2030 [1].

T2D is a disastrous disorder characterised by hyperglycemia as a result of insulin resistance, impaired insulin secretion or both. The pharmacological treatment of T2D include eight classes of approved oral anti-diabetic drugs (biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glucosidase inhibitors, amylin mimetics, glucagon-like peptide 1 mimetics and dipeptidyl peptidase 4 inhibitors). Insulin therapy is recommended for patients with initial HbA1c level greater than 9%.

Over 120 million people worldwide are prescribed metformin, a sole member of biguanide family drug as the first line oral anti-diabetic therapy owing to its safety profile and reduced risk of side effects. It has an exceptional therapeutic index for diabetes to treat hyperglycemia. It is considered as the gold standard anti-diabetic drug due to the insignificant risk of hypoglycemia and prescribed as first-line monotherapy. When metformin monotherapy fails to achieve the recommended standards of care like uncontrolled hyperglycemia, combinatorial therapy with one or two other anti-diabetic drugs along with ongoing metformin therapy is prescribed for effective glycemic control.

Use of metformin is effective in lowering glycosylated haemoglobin (HbA1c) by 1 to 2 percentage points when used as monotherapy or in combination with other anti-diabetic drugs [2]. Substantial evidence indicates that combinatorial therapy can establish superior glycemic control in most of the patients and targets key pathophysiological defects and help to achieve recommended targets in diabetes management. Nine classes of anti-diabetic drugs, their mechanism of action, rationale of combinatorial therapy and the list of combination drugs available in the market are discussed in Tables 1-3.

Metformin - Mode of action

Metformin from the biguanides family is an antihyperglycemic agent and is the drug of first choice to treat initially affected type 2 diabetic cases. It is a safer drug with multiple physiological and molecular effects associated with minimal toxicity. Metformin lowers hyperglycemia by reducing glucose absorption in intestine, increases glucose uptake in peripheral tissues and stimulates insulin secretion from pancreatic beta-cells.

Metformin acutely decreases hepatic glucose output by increasing insulin suppression of gluconeogenesis and reducing the energy supply through activation of AMP-activated protein kinase (AMPK) by inhibition of mitochondrial respiratory-chain complex 1 and consequent increase in NADH oxidation and ultimate reduction in synthesis of ATP (Figure 1).

This mechanism induces glucose uptake into muscle cells, thus lowers the fasting blood glucose in T2D patients [3], (Figure 2). Metformin also regulates its effect in the indirect inhibition of insulin receptor expression and tyrosine kinase activity, thereby enhancing insulin sensitivity and reducing insulin resistance in diabetic patients [4,5].

Sulfonylureas [SU] – Mode of action

SU are the oldest and most widely used medications for the treatment of T2D. These are the insulin secretagogues that enhance pancreatic islet cell function by stimulating insulin secretion from

beta-cells, thereby decreasing hepatic glucose production and effectively lowering blood glucose concentrations accompanied by reduction in HbA1c. They also act on the liver, inhibits the production of glucose by stimulating the glycolytic pathway [6].

Drug class	Drug name	Mechanism of action
Biguanides	Metformin	Suppresses gluconeogenesis Reduces glucose absorption in intestine Increases glucose uptake in peripheral tissues Stimulates insulin secretion
Sulfonylureas	Glibenamide, Glimpiride, Glipizide, Glicazide	Stimulates insulin secretion
Thiazolidinediones	Pioglitazone, Rosiglitazone	Increases glucose uptake by skeletal muscle Enhances insulin sensitivity in liver and adipose tissue Rejuvenate Beta cell function
DPP4-Inhibitors	Vidagliptin, Saxagliptin, Sitagliptin	Improves insulin secretion Suppress glucagon secretion
Meglitinides	Repaglinide, Nateglinide	Early insulin secretion
Alpha-glucosidase inhibitors	Acarbose, Miglitol	Inhibits carbohydrate absorption in the small intestine Blocks oligosaccharide catabolism
GLP1-mimetics	Exenatide, Liraglutide	Suppresses glucagon secretion
Amylin mimetics	Pramlintide	Delays glucose absorption from intestine
Insulin	Insulin	Physiological insulin release

Table 1: Antidiabetic drugs and their mechanism of action.

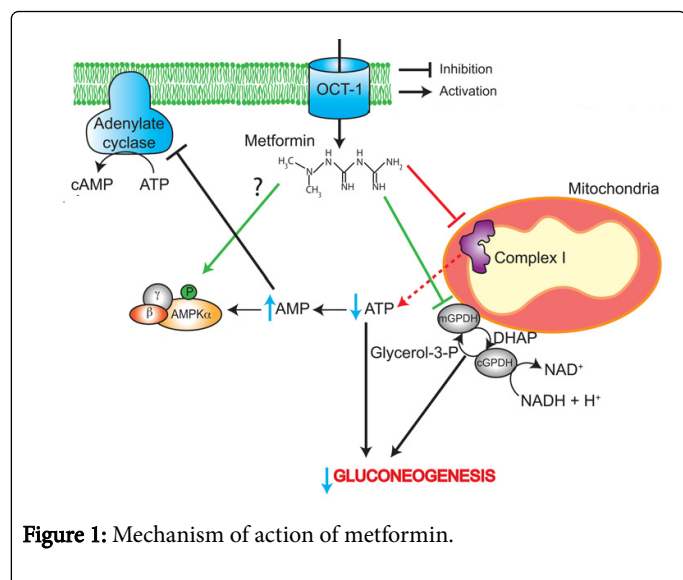


Figure 1: Mechanism of action of metformin.

SU bind to ATP-dependent K⁺(K-ATP) channel, which is an octameric complex of the inward-rectifier potassium ion channel Kir6.2 and sulfonylurea receptor SUR1 which associate with a

stoichiometry of Kir6.24/SUR14 on the cell membrane of pancreatic beta-cells and inhibits potassium efflux, thereby causing the electrical potential to become positive, thus the voltage-gated Ca²⁺ channels are opened leading to intracellular rise in calcium which further leads to increased fusion of insulin granules with cell membrane and finally secretion of insulin from beta-cells [7].

Treatment with SU is associated with a progressive linear decline in beta-cell function [8,9]. Eventual inability to maintain glycemic control reflects an advanced stage of beta-cell failure, thereby leading to hypoglycemia, the most common and most serious adverse event associated with SU therapy. The hypoglycemia episodes can be significant leading to coma or seizures and are seen more often in the elderly.

SU combinatorial therapy with metformin

Due to the adverse effects associated with the use of SU, combinatorial therapy has been focused mainly on adding metformin drug. Metformin and sulfonyl combinatorial therapy is associated with reduced mortality [10,11]. Metformin lowers blood glucose by decreasing hepatic glucose production and by increasing peripheral glucose utilization. SU induces insulin secretion from pancreatic beta-cells [12]. Combining both these drugs at an early stage that act by different individual mechanisms has an advantage of improving

glycemic control effectively. This has the potential advantage of increasing the therapeutic effectiveness of both these agents and decreasing the side effects if lower doses could be used.

In an UKPDS experimental study, it has been demonstrated that addition of metformin to SU therapy has increased the proportion of patients who could attain FPG criterion of diabetes (i.e., <40 mg/dl). This study has shown that early progression to metformin and SU combinatorial therapy benefits in maintaining better blood glucose

control that is not possible with single agents. The combination of both these drugs can attain a greater reduction in HbA1c (0.8-1.5%) than either of the monotherapies.

In a study by Reaven GM, et al. administration of 2.5 g/day metformin to sulfonylureas significantly lowered the fasting plasma glucose concentration (12.4 ± 0.8 vs. 8.8 ± 0.7 mmol/l), mean hourly postprandial plasma glucose concentration from 0800-1600 h (14.0 ± 1 vs. 9.4 ± 0.9 mmol/l), and HbA1c ($12.3 \pm 0.6\%$ vs. $9.0 \pm 0.6\%$) [13].

Drug class combinations	Drug combinations	Mechanism of action	Rationale
Biguanide + Sulfonylureas	Metformin + Glibenclamide	Metformin suppresses hepatic gluconeogenesis thus reducing fasting glycemia. Sulfonylureas stimulates insulin secretion from pancreatic beta cells	Provides synergistic effect, reduced mortality, decreases side effects
Biguanide + Thiazolidinediones	Metformin + Pioglitazone	Pioglitazone increases insulin sensitivity in liver and adipose tissue and pancreatic inhibits beta cell loss	Provides synergistic effect, prescribed as late add-on therapy, reduces weight gain
Biguanide + DPP- IV Inhibitors	Metformin + Vidagliptin	Improves insulin secretion from beta cells, decreases output of glucose from pancreatic alpha cells and decreases hepatic gluconeogenesis	Safety and tolerability (used for early combinatorial therapy), Synergistic effect
Biguanide + Meglitinides	Metformin + Repaglinde	Controls postprandial hyperglycemia	Provides synergistic effect
Biguanide + Alpha glucosidase inhibitors	Metformin + Acarbose	Blocks oligosaccharide catabolism, reduces intestinal glucose absorption thus controls postprandial blood glucose	Synergistic effect
Biguanide + GLP1-mimetics	Metformin + Exenatide	Suppresses glucagon secretion thus lowers postprandial blood glucose	Synergistic effect
Biguanide + Amylin mimetics	Metformin + Pramlintide	Suppresses release of glucagon from pancreatic alpha cells, delays absorption of glucose from intestine	Synergistic effect
Biguanide + Insulin	Metformin + Insulin	Physiological insulin release	Reduces weight gain

Table 2: Combinatorial therapy with metformin and other antidiabetic drugs.

Combination of drugs
Glimepiride + Metformin
Glipizide + Metformin
Glicazide + Metformin
Saxagliptin + Metformin
Sitagliptin + Metformin
Vidagliptin + Metformin
Voglibose + Metformin
Metformin + Rosiglitazone
Pioglitazone + Metformin
Metformin [SR] + Glimepiride + Pioglitazone
Metformin + Glimepiride + Pioglitazone

Table 3: List of antidiabetic combination drugs available in the market.

Thiazolidinediones (TZDs) – Mode of action

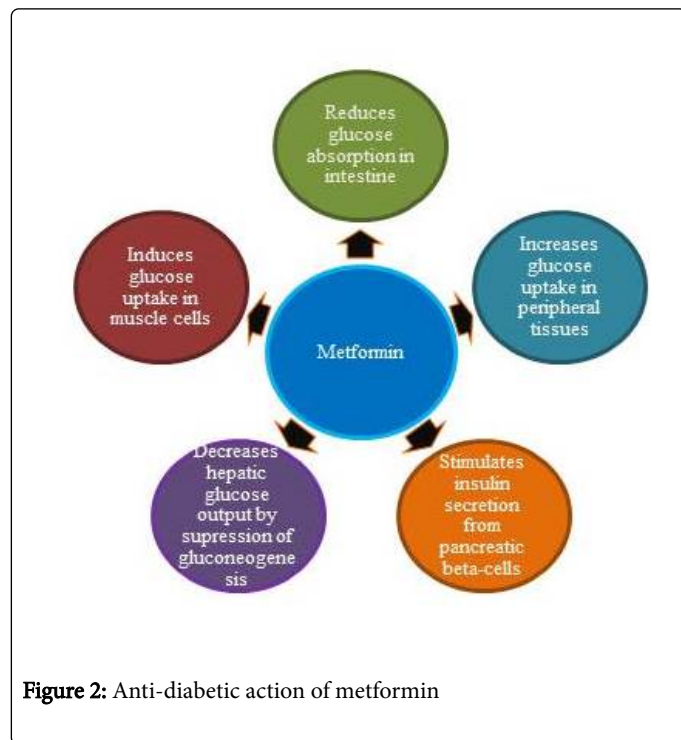
TZDs bind to peroxisome proliferator-activated receptors (PPARs), a ligand co-activated transcription factor involved in glucose and lipid metabolism. PPARs exist in several different forms: PPAR- α , PPAR- δ , and PPAR- γ . PPAR- γ is the major target of TZDs, and these receptors are expressed throughout the body in many different tissues, macrophages, and endothelial cells, beta- cells of the pancreas and predominantly in adipose tissue [14]. The drug-PPAR- γ complex stimulates the production of proteins like adiponectin that enhances insulin sensitivity [15]. Partial insulin sensitivity can be enhanced by activation of AMPK.

TZDs rejuvenate beta cell function thereby delaying progression of the disease and reduce insulin resistance and exhibit no effect on insulin secretion. TZDs lower fasting and postprandial hyperglycemia, fasting insulin levels, free fatty acids suggesting that these drugs improve insulin sensitivity [16].

TZDs combinatorial therapy with metformin

TZDs are prescribed as second line therapy or late add-on therapy as they show no effects on beta-cell function. TZDs should be used in combination with other drugs [17]. Metformin improves insulin sensitivity through the activation of AMPK in liver; TZDs improve insulin sensitivity through activation of PPAR- γ in adipocytes. Due to

their different sites of action and different cellular mechanisms, this combination results decrease in HbA1c and attains a potential additive and synergistic effect on insulin resistance. The major side effects associated with TZDs include weight gain and fluid retention which typically manifests as peripheral edema. Hence, weight gain can be minimized by using TZDs combined with metformin [18]. Metformin and TZDs combination exhibits cardiovascular benefits also.



Apart from enhancing glycemic control, these drugs lower triglycerides levels, increases high-density lipoprotein cholesterol (HDL) levels, and increases the low-density lipoprotein cholesterol (LDL) particle size. The most commonly approved TZDs in combination with metformin are pioglitazone and rosiglitazone [19]. These drugs have been shown to produce similar reductions in HbA1c of approximately -1.6%, with reductions ranging from -1.2% to -2.3% over 3-12 months of therapy [20-25].

Fixed dose levels of pioglitazone-metformin are approved (15 mg/500 mg and 15 mg/850 mg) for treatment of patients who failed to achieve monotherapy with metformin [26]. In Europe and US, single pill combinations of both pioglitazone-metformin and rosiglitazone-metformin are available in the market [27]. This kind of combination in the same pill often leads to improvement in patient compliance and a decrease in cost.

Dipeptidyl peptidase-IV [DPP-IV] inhibitors – Mode of action

Ingestion of food leads to higher levels of active incretins, the naturally occurring two intestinal glucoregulatory hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) released from small intestine throughout the day. The physiological actions of glucagon-like peptide-1 (GLP-1) includes sensitization of beta-cells, augmentation of glucose stimulated insulin secretion, inhibition of glucagon secretion, thereby reducing the circulating glucose levels and stimulation of insulin biosynthesis

[28,29]. These two incretin hormones play a major role in the postprandial hyperglycemia, for up to 70% of the total insulin is secreted in response to a meal.

In T2D patients, incretin function may be impaired, which leads to reduced postprandial insulin secretion and inadequate glucagon suppression that contribute to postprandial hyperglycemia [28]. DPP-IV inhibitors improve insulin secretion and suppress glucagon secretion by glucose-dependent mechanisms by promoting glucose homeostasis through inhibition of DPP-IV, the key enzyme, responsible for degradation of GLP-1 and GIP. Sitagliptin, vildagliptin and saxagliptin and linagliptin (gliptins) are the licensed agents currently in use for DPP-IV inhibitors.

DPP-IV inhibitors combinatorial therapy with metformin

Progressive decline in beta-cell function is associated in T2D. Vildagliptin improves glycemic control through physiological mechanisms that result in an attenuation of beta-cell decline [30-33]. Vildagliptin prolongs the action of incretins, works in a unique way and improves insulin secretion from the beta-cells of the pancreas and decrease the output of glucagon from the alpha-cells which results in the decrease of hepatic gluconeogenesis.

In an experimental study of 36 patients who were under medication of vildagliptin 50 mg and metformin 500 mg twice daily, the FPG and PPG values were found to be reduced by -76.93 ± 66.55 and reduction in HbA1c levels by -0.58 ± 0.67 [34,35]. So in patients with T2D the add on of vildagliptin 100 mg to metformin 1000 mg caused a greater reduction in HbA1c [36,37]. The addition of low dose combination of vildagliptin to metformin shows synergistic effect in reducing FPG, PPG and HbA1c.

In a VISION study in Chinese patients, the early use of combinatorial therapy of vildagliptin with ongoing metformin therapy achieved target glycemic goals and improves islet-cell function during fasting stage [37,38]. Saxagliptin at 2.5 mg, 5 mg dosage in combination with 10 mg metformin decreased HbA1c by 0.59%, 0.69%, and 0.58%, respectively [38]. Sitagliptin enhances the postprandial GLP-1 response in a glucose-dependent manner and increases post-meal insulin secretion.

Meglitinides – Mode of action

Glinides are the short acting non-sulfonylureas insulin secretagogues that stimulate the pancreas to produce insulin in response to ingested glucose. Due to their shorter duration of action, they are used as 'prandial drugs' taken just before meals and must be administered more frequently. Two glinides repaglinide and nateglinide are currently in use; of these two glinides, repaglinide is less effective in lowering HbA1c than nateglinide [39]. They act via the ATP dependent potassium channels in pancreatic beta-cell receptors similar to SUs and increases insulin release.

Repaglinide

Repaglinide is the first meglitinide; it stimulates early insulin secretion during postprandial period and causes reduction of postprandial hyperglycemia and reduced HbA1c. It stimulates insulin secretion by blocking ATP-dependent potassium channels (K-ATP) of the pancreatic beta-cell, which is a hetero-octameric complex composed of two different protein subunits, an inwardly rectifying K⁺ channel (KIR) subunit 6.x and a sulfonylurea receptor (SUR). More

than one isoform exists for both Kir6.x (Kir6.1, Kir6.2) and SUR (SUR1, SUR2A, and SUR2B). These subunits Kir6.2 and SUR1 are predominantly expressed in pancreatic beta-cells.

The blocking of K-ATP channels results in depolarization of membrane and influx of calcium through voltage-gated calcium channels leading to an increase in intracellular calcium and subsequent exocytosis of insulin-containing granules [40].

Nateglinide

Nateglinide is a derivative of phenylalanine. Molecular studies have revealed that the binding site of nateglinide is different from that of repaglinide [41]. Nateglinide binds competitively to SURs, inhibits K-ATP channels more rapidly enhancing at a 16-fold when the glucose concentration is raised from 3 mmol/l to 16 mmol/l and shows a higher degree of specificity for SUR1 over SUR2 in a shorter duration of action and stimulates insulin secretion compared to repaglinide where the potency of repaglinide is enhanced 4-fold only. The pharmacodynamic properties of nateglinide are very much unique in several aspects.

The half-life of nateglinide on the receptor is approximately 2 s, very much shorter than that of repaglinide, which is ~3 min. The dissociation from the receptor is 90 times faster when compared to that of repaglinide. It indicates a very short on-off effect of nateglinide on insulin release. Pharmacodynamic studies in T2D patients have revealed that the nateglinide when administered before meals induces early phase insulin secretion and reduces post-prandial hyperglycemia in a dose-dependent manner [42]. Insulin secretion was significantly greater when repaglinide was taken prior to a meal than nateglinide administered in the fasted state [43].

Meglitinides combinatorial therapy with metformin

Metformin regulates basal glucose levels and repaglinide targets postprandial glucose levels, hence the combinatorial therapy of repaglinide with metformin having complementary mechanisms of action are recommended by AACE/ACE for the management of hyperglycemia in patients with HbA1c levels, 9.0%.

Clinical data have shown there is an excellent improvement in glycemic control with combination of repaglinide and metformin over a 4 to 5 months. In a study conducted by Moses et al. [45] metformin and repaglinide combination groups has shown a significant reduction in HbA1c from 8.3% (67 mmol/l) to 6.9% (52 mmol/l) whereas alone metformin and repaglinide groups has shown a remission from 8.6% (70 mmol/l) to 8.3% (67 mmol/l) and from 8.6% (67 mmol/l) to 8.2% (66 mmol/l) respectively [44,45]. Due to their effective combination in maintaining blood glucose, USA has approved this combinatorial therapy in 1997 and in Europe in 1998. In a phase III study in Japanese patients for 16 weeks, HbA1c was reduced by approximately 1% from baseline in patients with metformin and repaglinide combinatorial therapy and achieved significant control in PPG, FPG and postprandial serum insulin [46].

The combination of nateglinide to basal insulin combined with metformin might help in controlling postprandial hyperglycemia. In a study of initial combinatorial therapy of nateglinide with metformin by Horton et al. the patients has shown a significant reduction in HbA1c from a mean baseline of $8.2 \pm 0.1\%$ than 0.8% reduction with both monotherapies. Seventy percent of the patients achieved a target HbA1c of <7.0% in nateglinide and metformin combination patients and also FPG and PPG values also reduced [47].

Alpha-glucosidase inhibitors (AGI) - Mode of action

AGI are competitive inhibitors that inhibit alpha-glucosidase enzymes found in the brush border cells lining the small intestine and blocks the oligosaccharide catabolism thus lowering postprandial hyperglycemia and enabling the beta-cells of pancreas to compensate for the first phase insulin secretory defect.

Acarbose and miglitol were the first alpha-glucosidase inhibitors approved in mid-1999 in the U.S. Miglitol, derived from 1-deoxynojirimycin are the first pseudomonosaccharide AGI. Voglibose is weaker at inhibiting sucrase and inhibits most alpha glucosidase enzyme and has minor effect on pancreatic amylase whereas acarbose is an inhibitor of intestinal sucrase and pancreatic amylase [48]. These drugs are administered at the beginning of each meal, and are contraindicated in patients with diseases such as inflammatory bowel disease, partial bowel obstruction, and in severe renal or hepatic disease.

AGI combinatorial therapy with metformin

Hypoglycemia is not typically associated with monotherapy with the alpha-glucosidase inhibitors; hence it is approved as combinatorial therapy with metformin. Acarbose delays glucose absorption and thus attenuates postprandial rises in and blood glucose and insulin.

Metformin suppresses hepatic glucose production. Acarbose in combination with metformin has been shown to improve HbA1c measurement by 0.8% [49], 0.65%, and 0.9% [50]. It has been reported that the combination of acarbose to metformin in sub-optimally controlled patients reduced HbA1c by about 0.8-1.0% [47].

In an observational GLOBE study by Saboo et al., the combination treatment with acarbose/metformin has shown a significant reduction in HbA1c, FBG and PPG by -1.0%, -42.4 mg/dl, and -80.2 mg/dl, respectively [51]. In another study, acarbose/metformin fixed dose combination (FDC) therapy significantly reduced HbA1c by -1.35%; FPG by -29.5mg/dl, PPG by -41.6mg/dl from baseline. More patients treated with acarbose/metformin FDC achieved HbA1c<7.0% [47.8% vs. 10.7%] [52]. In a study by Rosenstock et al. mean HbA1c achieved a significant reduction by 0.65% in acarbose add-on therapy to metformin [22].

Glucagon like peptide mimetics (GLP-1 mimetics) -Mode of action

GLP-1 mimetics are also known as GLP-1 receptor agonists. GLP-1 is rapidly degraded by DPP-IV enzyme which reduces half-life, thereby limiting its effects, hence may not be given therapeutically. To provide resistance to rapid degradation of GLP-1, GLP-1 mimetics and GLP-1 analogues are given as an injection for therapeutic use which provides longer half-lives than native hormone. On pancreatic beta-cells GLP-1 mimetics bind to GLP-1 receptors, this binding leads to have a longer half-life as the DPP-IV enzyme cannot degrade the homologue or analogue peptides as rapidly as native GLP-1.

GLP-1 mimetics combinatorial therapy with metformin

Exenadin and Liraglutide are the first generation GLP-1 analogues. Exenadin-4 (exenatide) is the first developed GLP-1-agonist, improves glycemic control similar to the endogenous GLP-1 hormone. Exenatide suppresses glucagon secretion. It is administered subcutaneously twice daily. HbA1c levels are lowered by 0.5-1%, mainly by lowering postprandial blood glucose levels [53].

The add-on therapy of exenatide or rosiglitazone or both with a stable metformin dose in an open-label study in 73 T2D patients has shown controlled mean HbA1c level, 7.8%. [54]. Randomized clinical trials of exenatide in combinatorial therapy with metformin in different dosages have shown a significant reduction in HbA1c [55].

Liraglutide is a GLP-1 analogue with 97% sequence similar to the human hormone. Due to its structural modifications, it results in reversible albumin binding leading to prolonged duration of action with reduced susceptibility to DPP-IV. It is injected once daily, it reduces fasting blood glucose and glycemic excursions associated with all meals. Liraglutide combined with metformin shows reduced mean HbA1c levels by more than 1% over 26 weeks [56-58].

Amylin mimetics - Mode of action and combinatorial therapy with metformin

Amylin is an amino acid polypeptide hormone produced by the pancreas that is co-localized and co-secreted with insulin in small amounts which slows down the movement of food through the intestine. This suppresses the release of glucagon from pancreatic alpha-cells and delays the absorption of glucose from the intestine which reduces sudden increase in blood glucose. Amylin mimetics are synthetic drugs that are administered before meals; they act like amylin hormone and benefits in weight loss, reducing HbA1c, blood glucose levels and delays gastric emptying [59].

Pramlintide is a synthetic human amylin analogue, a beta-cell peptide co-secreted with insulin. This has the same actions of native amylin. Pramlintide therapy is not clear as it requires three self-injections daily. At the beginning of the pramlintide therapy, nausea, diarrhoea and headache are the severe side effects. Combination of pramlintide with metformin shows a significant reduction in HbA1c [60].

Combination of metformin with insulin

Due to progressive deterioration of pancreatic beta-cell function, oral hypoglycaemic agents often fail to maintain adequate glycemic control after few years of treatment. Insulin and metformin combination was more effective than the other combinations shown by a greater reduction in HbA1c after 12 months of treatment and also put on less weight than the other groups [61,62]. Combinatorial therapy with insulin usually refers to the use of daytime oral anti-diabetic agents together with a single injection of intermediate or long-acting insulin at bedtime.

Metformin is usually continued even though the patient is on insulin therapy because it reduces cardiovascular risk in patients with T2D who are overweight. Metformin combined with insulin is associated with decreased weight gain, a lower insulin dosage, and less hypoglycemia when compared with insulin therapy alone. Hence, the efficacy of combinatorial therapy of metformin with other anti-diabetic drugs might have significant achievement in glycemic control.

The landscape combination treatment for management of hyperglycemia in T2D may not achieve desired glycemic goals due to adherence, poor compliance, and persistence to suggested anti-diabetic therapy, flexibility of time of administration and frequent dosages. In order to achieve target glycemic index, improved adherence, decreased incidence of adverse drug reactions, strategies are required for the optimal management of the disease. This problem can be managed by prescribing fixed dose combination drugs (FDCs). The early shift into fixed dose combinatorial therapy is efficient in maintaining glycemic goals and has a chance of preventing diabetic complications.

Fixed dose combination drugs [FDCs]

FDCs are oral pharmaceutical combination formulations with fixed amounts of two or more than two active drugs in a single pill. Use of FDCs reduces prescriber flexibility, simplifies dosage titration along with advantages like ease of administration, convenience, and reduces the pill burden and capital investment. The relative benefits of FDCs compared to monotherapy and combination therapy are discussed in Table 4.

The main aim of T2D treatment is to achieve good glycemic control and to minimize the risk of diabetic complications, macro and micro vascular disorders. The diabetic subjects worldwide rises to double in the next 20 years, as a result of increasing obesity and hypertension [58].

Hence, the development of FDCs of anti-diabetic agents, anti-obesity agents, anti-hypertensive agents and statins [in a single pill-Polypills] can be established to reduce the economic burden which provides an expedience for extra medication without extra tablets.

Several FDC drugs have been developed and available in the market (Table 5). FDCs or polypills when administered in the early onset of the disease might help in improving therapeutic outcomes in diabetes and prevent complications.

Relative benefits	Monotherapy	Combinatorial therapy (free drug combinations)	Fixed dose combinatorial therapy
Response rate	Low	High	High
Dosage simplicity	Simple	Complex	Simple
Compliance	Medium	Medium	High
Tolerability	Medium	High	High
Titration flexibility	High	High	Medium
Ease of administration	Simple	Complex	Simple
Convenience	Simple	Complex	Simple
Cost	Medium	High	Medium

Table 4: Relative benefits of Monotherapy, Combinatorial therapy and FDC therapy

Fixed dose combination of anti-diabetic drugs
Metformin, 500 mg+Glyburide, 5 mg
Metformin, 500 mg+Glipizide, 5 mg
Rosiglitazone, 500 mg+Metformin, 2 mg

Table 5: Fixed dose combination of antidiabetic drugs

Conclusion

T2D is a high profile public health burden reaching pandemic proportions worldwide. Prevention and management of this disease has become a major issue these days and is a special subject in chronic medicine. The main aim is to optimize treatment, personalized management and prevent complications of diabetes. A determined fixed dosage combination drugs for an individual promotes personalized management of T2D reducing pill burden on patients and improving adherence to treatment. In future, extensive research is necessary to understand the potential role of pharmacogenetics in tailoring the safer personalized fixed dose combinatorial therapy and poly pill administration for diabetics in reducing further complications.

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