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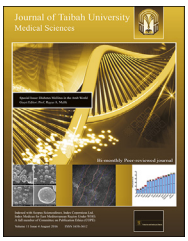

Review Article

Diabetes and oral therapies
A review of oral therapies for diabetes mellitus

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الملخص

تستخدم الأدوية الفموية الخافضة لسكر الدم لعلاج النوع الثاني من داء السكري منذ عقود، نظرا لفاعليتها وسهولة استعمالها. الأدوية الخافضة لسكر الدم الأكثر تجربة هي متفورمين وسلفونيل يوريا منذ أكثر من ٥٠ عاما. تلى هذه الأدوية تقديم مركبات أخرى من أدوية خفض سكر الدم مثل الجلينيدات، وثيازولدين ديونات، ومثبطات ألفا جلوكوسيديز، ومثبطات ديببتديل ببتديز ٤—، ومثبطات الناقل المشارك لصوديوم —جلوكوز —٢. ويعتبر المتفورمين الدواء المفضل للعلاج المنفرد، مالم يكن هناك مانع من استخدامه أو وجود آثار جانبية له. وقد أدى نقص السكر في الدم الناجم عن السلفونيل يوريا إلى تراجع استخدمه لصالح بعض المركبات الجديدة، ولكن الوصفة العامة لسلفونيل يوريا مع ميتفورمين رخيصة جدا ومازالت فاعلة. والجدير بالذكر أن مخاطر القلب والأوعية الدموية للعديد من الأدوية هي مصدر قلق كبير للأطباء وهيئات التشريع. كما يجب على الطبيب المعالج أن يضع في اعتباره حالة المريض الصحية، والآثار الجانبية للأدوية، والتكلفة، وما يفضله المريض عند اختيار الأدوية الخافضة لسكر الدم للعلاج المزدوج أو الثلاثي. تستعرض هذه المقالة المزايا والعيوب لمجموعة من الأدوية الفموية الخافضة لسكر الدم وتطبيقاتها للعلاج المنفرد أو المتعدد.

الكلمات المفتاحية: سلامة الدواء؛ علاج نسبة السكر في الدم؛ أدوية خفض سكر الدم؛ حوادث القلب والأوعية الدموية؛ العلاجات الجديدة المضادة للسكري

Abstract

For decades, antihyperglycaemic agents have been used for the treatment of type 2 diabetes mellitus given their effectiveness and convenience. Metformin (MET) and sulphonylureas (SU) are time-tested antihyperglycaemic agents that have been administered for more than 50 years. These agents were followed by the introduction of other antihyperglycaemic agents such as glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), dipeptidyl peptidase-4 inhibitors (DPP-4I), and sodium–glucose cotransporter-2 inhibitors (SGLT2I). MET is recognized as the drug of choice for monotherapy unless contraindicated or unwanted side effects occur. SU-induced hypoglycaemia is losing ground to various new agents, but the generic formulae of SU together with MET are cheap and effective. The cardiovascular hazards of several agents are a major concern to physicians and legislating bodies. In choosing antihyperglycaemic agents for dual or triple therapy, the treating physician must keep in mind the health status of the patient, medication side effects, cost, and patient preference. This review addresses the advantages and disadvantages of a range of antihyperglycaemic agents and their applications in monotherapy or combination therapy.

Keywords: Cardiovascular events; Drug safety; Glycaemic management; Hypoglycaemic agent; New antidiabetic therapy

Introduction

Oral antihyperglycaemic agents have been the mainstay of treating type 2 diabetes mellitus (T2DM) for numerous decades given their efficacy and convenience. Metformin (MET) and sulphonylureas (SU) have been in use for more than 50 years, and their major side effects are widely

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known. The last two decades have witnessed the introduction of many classes of these agents, and their optimal use and side effects are gradually recognized. Seven approved major classes of oral antihyperglycaemic agents are currently available: MET, SU, glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), dipeptidyl peptidase-4 inhibitors (DPP-4I), and the most recent sodium−glucose cotransporter-2 inhibitors (SGLT-2I). This review summarizes the characteristics of each class and their use in T2DM management. The cardiovascular safety of these medications has received more attention in the last few years after the United States Food and Drug Administration (FDA) reported unexpected cardiovascular outcomes and made new requirements for licensing new antidiabetic drugs. These outcomes are discussed in the section on TZD.

Metformin

Traditional medicine used French lilac for treating diabetes for centuries, and guanidine compounds were derived from its extract in 1920s.[1] These compounds exhibited hypoglycaemic effects in animals but were later withdrawn due to hepatotoxicity in patients. The biguanides, phenformin and MET are derived from guanidines and were introduced in 1950's.[2] However, phenformin was withdrawn in the late 1970s, as it was linked to fatal lactic acidosis.[3]

Mechanism of action and efficacy

Metformin works by reducing hepatic gluconeogenesis and increasing glucose uptake in the peripheral tissues, especially in muscles,[4,5] thus improving insulin sensitivity. As it does not stimulate insulin secretion, metformin monotherapy rarely causes hypoglycaemia. Metformin also enhances the action of glucagon-like-peptide-1 (GLP-1), but the clinical significance of this agent is not established.[6]

Metformin is recognized as the first agent to be used as monotherapy with life-style modification to treat T2DM unless intolerance or a contraindication for its use is noted.[7,8]

The United Kingdom Prospective Study (UKPDS) demonstrated that overweight patients allocated to the MET group exhibited reduced median HbA1C compared with the conventional group (7.4% vs 8%), with 32% risk reduction for any diabetes related endpoints.[9] A systemic review analysing the results of 15 controlled studies on treatment with MET versus control reported a weighted mean absolute difference (WMAD) in HbA1C levels of −1.14%.[10] Many reports refer to a reduction of HbA1C by 1−2%.[11] Despite this finding, metformin gradually loses efficacy with a cumulative incidence of secondary failure as a monotherapy of 21% at 5 years, which is better compared with SU.[12] However, starting MET monotherapy in T2DM was less likely to require intensification by another agent compared with SU, TZD, or DPP-4I.[13]

Analysis of 8 controlled trials reported the weighted mean difference (WMD) in body weight between the treatment and control as 0.3 kg.[10] Although some studies reported weight reduction, the treatment is generally considered weight neutral.[11]

Side effects and contraindications

The most frequently reported side effect, which may force the patient to discontinue usage, is gastrointestinal (GI) upset, which could be due to the release of 5-hydroxytryptamine and other substances within the duodenal mucosa.[14]

GI upset may be managed by a starting dose of 500 mg daily with meals. The dose is then increasingly titrated by 500 mg every 1−2 weeks in two to three divided doses until the desirable dose is achieved. Another method involves the use of the extended release formula of MET. The extended release formula was well tolerated by 97.4% of patients in a study of 3556 patients.[15] Vitamin B12 deficiency may develop with prolonged MET use, especially in elderly diabetic patients administered high doses.[16]

Lactic acidosis is a lethal complication that causes the withdrawal of phenformin, but this condition rarely occurs with MET. An extensive systematic review showed no increase in lactic acidosis in 70,490 MET users years compared to non users.[17] However, one should avoid using MET in conditions that predispose to lactic acidosis, such as severe renal failure. Metformin should be avoided in patients with chronic liver disease, heart failure, renal failure, sepsis and shock.[11] However, there is debate about avoiding MET in heart failure. Analysis of nine cohort studies concluded that MET is as safe as other oral hypoglycaemic agents in patients with heart failure.[18]

The FDA advises to avoid MET if serum creatinine is $\geq$1.5 mg/dl in males and $\geq$1.4 mg/dl in females.[19] However, an observational study over approximately 4 years revealed no increase in the risk of severe side effects, including acidosis, in patients administered MET with a creatinine clearance of 30−45 ml/min/1.73 m^2.[20]

The FDA also advises to avoid MET before, during and 48 h following radiologic studies involving IV iodinated contrast.[19] However, the American College of Radiology does not recommend holding MET dosing in relation to IV iodinated contrast studies if the patient does not have acute kidney injury and has an eGFR $\geq$30 ml/min/1.73 m^2 nor in relation to gadolinium in the typical dose range of 0.1−0.3 mmol/kg.[21]

The side effects of MET are summarized in Table 1.

Cardiovascular safety

Metformin was associated with 42% reduction in diabetes-related deaths and 36% reduction of all-cause mortality in the UKPDS.[9] In the intensive blood-glucose control group, patients treated with MET exhibited a greater effect for all-cause mortality, stroke and diabetes related endpoints compared with those treated with SU. The reduction of myocardial infarction and mortality gained by MET use in overweight patients in the UKPDS was maintained 10 years after the end of the study.[8]

Dosage

Table 2 shows the dose of MET and relation to food intake.

Table 1: Side effects of antihyperglycaemic agents.

Drug	Body weight	Hypoglycaemia[a]	Others
Metformin	Neutral	Neutral	GI upset, rarely lactic acidosis. Avoid in severe renal and heart failure.
Sulphonylureas	Increased weight	Yes	Questionable cardiovascular safety, care in liver disease.
Glinides	Increased weight	Yes	Drug interactions, upper respiratory infections.
Thiazolidinediones	Increased weight	Neutral	Oedema, heart failure, bone loss
Alpha-glucosidase inhibitors	Neutral	Neutral	GI upset. Avoid in liver cirrhosis and inflammatory bowel disease.
Dipeptidyl peptidase-4 inhibitors	Neutral	Neutral	Angio oedema, pancreatitis.
Sodium−glucose cotransporter-2 inhibitors	Decreased weight	Neutral	Genitourinary infections, dehydration

GI: Gastrointestinal.
[a] Hypoglycaemia in monotherapy.

Sulphonylureas

The discovery of sulphonamides marked the beginning of the SU era. In 1942, a sulphonamide developed to treat typhoid fever was found to cause hypoglycaemia in animals and caused severe hypoglycaemia in patients.[1,22] This discovery was followed by the development of tolbutamide in 1956 and chlorpropamide thereafter. First-generation SUs, namely, tolbutamide and chlorpropamide, are not currently used and were replaced by second generation SUs, including glibenclamide, glipizide, gliclazide, and glimepiride.

Mechanism of action and efficacy

Sulphonylureas exert their hypoglycaemic effect by increasing second phase insulin secretion.[23] The action of SUs may be longer than their half-life given the biologic activity of their metabolites.

Sulphonylureas are effective antihyperglycaemic agents that reduce HbA1C by greater than 1% in monotherapy regimens.[11] Analysis of 11 controlled studies of monotherapy with SU against control found that the WMAD in HbA1C was −1.52.[10] The UKPDS demonstrated the effectiveness of SU over a 10-year period. In this study, the intensive group achieved an HbA1C of 7% with a 25% reduction in microvascular complications and 10% reduction in any diabetes-related death. However, no beneficial effects on macrovascular complications were noted.[24] Despite their efficacy, the efficacy of sulphonylureas in monotherapy is gradually reduced. The cumulative incidence of secondary failure for glibenclamide was 34% at 5 years.[12]

Side effects and contraindications

The effectiveness of oral administration, the convenient once or twice daily dosing and greater than 50 years of testing make SUs appealing oral antihyperglycaemic agents, but their efficacy is hampered by side effects. The most important side effects include hypoglycaemia and weight gain. In the intensive group of the UKPDS, major hypoglycaemia was noted to be 1% per year in the chlorpropamide group, 1.4% in the glibenclamide group and 1.8% in the insulin group, with significant corresponding increases in weight of 2.6 kg, 1.7 kg and 4 kg, respectively.[24] The hypoglycaemia may be characterized as late postprandial or fasting the second phase of insulin secretion is stimulated. Hypoglycaemia may follow exercise as with insulin and other insulin secretagogues. As SUs are metabolized in the liver, they must be administered with caution in patients with liver dysfunction.[25]

Treating physicians may be concerned about using SU if the patient experienced a previous allergy to sulphonamides. One report suggested that the determinant of type 1 allergic reactions to sulphonamides is the N1 heterocyclic ring, which is lacking in non-antibiotic sulphonamides, and that SUs may be used in such patients.[26]

However, if a patient experienced a serious reaction, such as Steven-Johnson's syndrome, it may be better to avoid SUs as the reaction may be T-cell mediated. The side effects of SU are summarized in Table 1.

Cardiovascular safety

Although the UKPDS reported reduced mortality in the SU arm of intensive treatment, many authorities are concerned that SUs have not been subject to rigorous cardiovascular evaluation.[27] This concern was raised as early as 1970 when a report from the University Group Diabetes Program (UGDP) found that the mortality of non-insulin-dependent patients treated with tolbutamide was approximately 2 $^{1}/_{2}$ that of those treated with diet alone.[27,28]

In the Diabetes Audit and Research in Tayside Scotland study (DARTS), the adjusted relative risks of mortality and cardiovascular mortality in patients on SU monotherapy were 1.43 (95% CI 1.15−1.77) and 1.7 (95% CI 1.18−2.45), respectively.[29] Similarly, in a cohort study of 98,665 veterans on SU monotherapy, the adjusted hazard ratio of CVD events was 1.21 (95% CI 1.13−1.30) compared with 155,025 patients on MET.[30]

The adjusted hazards ratio (HR) of death in patients administered high doses of glibenclamide monotherapy was 1.3 (95% CI 1.2−1.4) compared with those on lower doses.[31] Conversely, the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified release Controlled Evaluation (ADVANCE) trial reported no increase in major macrovascular events or death risk in patients on

modified release gliclazide and other agents in the intensive therapy arm that lowered HbA1C to 6.5%. However, macrovascular and microvascular events and death were increased in patients who had severe hypoglycaemia.[32]

This question should be settled by more rigorous studies. Metformin remains the first drug of choice for initiating T2DM treatment.

Dosage

The doses of different SUs and relation to food consumption are presented in Table 2. It is suggested that the therapeutic effect of SU may be achieved by doses lower than the specified maximum dose. For example, glipizide doses greater than 10 mg daily do not offer additional hypoglycaemic effects.[33] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended adding a hypoglycaemic agent from a different class if blood glucose is not controlled by a submaximal dose of insulin secretagogues rather than using the maximal dose.[34]

Glibenclamide and its metabolites may accumulate in patients with chronic kidney disease (CKD), and glibenclamide is associated with prolonged hypoglycaemia in such patients.[35] Thus, it is not recommended for patients with CKD. Severe hypoglycaemia as a result of glimepiride has been described in 37 patients with creatinine clearances of 38 ± 23 ml/min,[36] but the National Kidney Foundation (NKF) advises to start with a dose of 1 mg in patients with CKD instead of avoiding its use.[37]

The metabolites of gliclazide are inactive. Thus, hypoglycaemia is expected to occur less frequently in CKD patients administered gliclazide compared with glibenclamide and glimepiride.[35] The NKF advises no dose change in CKD patients. However, one has to observe patients with end stage renal failure carefully if gliclazide is administered. Glipizide is metabolized in the liver to inactive metabolites and is unlikely to produce hypoglycaemia in CKD patients. This drug is endorsed by the NKF as the SU of choice for patients with CKD. It seems logical that such patients experience better results with glipizide or gliclazide rather than glimepiride, which has been associated with severe hypoglycaemia in this population.[36]

Glinides

Repaglinide was the first member of this group, which was approved by the FDA in December 1997.[38] Nateglinide was approved in December 2000.

Mechanism of action and efficacy

This group of insulin secretagogues works through binding sites on beta cells that are both distinct and similar to those of SU.[39] These drugs work by stimulating first-phase insulin release but not second-phase release. Thus, these drugs are less likely to produce late or fasting hypoglycaemia compared with SUs.[40] These drugs exert this effect as they close the potassium channels of the beta cell and open the calcium channel, thus inducing insulin exocytosis.[39]

Repaglinide has a dose-dependent, rapid onset mechanism of action when taken 15 min before meals. Within 30 min of starting a meal, repaglinide produced a relative increase of insulin up to 150% with no residual effects 4 h later.[41]

Repaglinide is effective as monotherapy, reducing HbA1C by 1.14% in a trial with flexible meal dosing for 16 weeks.[42]

Table 2: Dose and monthly cost of antihyperglycaemic agents.

Medication	Adult daily dose	Food effect	Brand cost (SR)	Generic cost (SR)
Metformin: Immediate release	500 mg twice daily Maximum 3 g in 3 doses	During or after meals	60.00	21.00
Metformin: Extended release	750 mg once daily Maximum 2 g	With evening meals	75.00	NA
Glibenclamide: Immediate release	1.25–20 mg daily Doses ≥ 10 mg: divided twice daily	Taken with food	98.00	36.00
Glipizide: Immediate release	2.5–40 mg Doses ≥ 15 mg: divided twice daily	Take 30 min before meals	NA	NA
Gliclazide: Immediate release	80–320 mg daily Doses ≥ 160 mg: divided twice daily	Taken with food	NA	70.00
Gliclazide: Extended release	30–120 mg once daily	Taken with food	102.00	NA
Glimepiride:	1–8 mg OD	Take with food	142.00	71.00
Repaglinide:	0.5–4 mg with meals	15–30 min before meals	206.00	NA
Pioglitazone:	15–45 mg OD	Regardless of food	139.00	NA
Rosiglitazone	4–8 mg in 1 or 2 daily doses	Regardless of food	NA	NA
Acarbose:	25–100 mg	At the beginning of each meal	82.00	NA
Sitagliptin	100 mg daily	Regardless of food	150.00	NA
Saxagliptin	2.5–5 mg	Regardless of food	140.00	NA
Vildagliptin	50 mg BID	Regardless of food	150.00	NA
Linagliptin	5 mg twice daily	Regardless of food	113.00	NA

NA: Not available in KSA. OD = once daily. Cost calculated for 1 month supply of maximum dose.
SR = Saudi Riyals; 3.75 Riyals = 1 US Dollar.

In a meta-analysis of four trials, repaglinide treatment reduced HbA1C by a WMAD of 1.32% compared with controls.[10] However, the durability GLN hypoglycaemic benefits in monotherapy is not substantial. In a follow-up of new users up to 5.5 years, the HR for GLN failure compared with metformin was 1.66 (95% CI 1.37–2.0).[43]

This group is especially helpful when meals are irregular or unpredictable (e.g., elderly patients or patients fasting for Ramadan). However, the frequent dosing may be a drawback for some patients.

Side effects and contraindications

Similar to all insulin secretagogues, repaglinide may produce weight gain and hypoglycaemia at a frequency comparable to that of SU.[44] Repaglinide may also cause upper respiratory tract infections with a frequency similar to that observed with SU.[45]

Repaglinide is contraindicated in combination with gemfibrozil. This combination caused a significant increase in repaglinide exposure, but this effect is not observed with fenofibrate.[46] This class should be used with caution in the presence of liver disease.[11] Repaglinide side effects are summarized in Table 1.

Cardiovascular safety

Glinides have not been subjected to large prospective studies to verify their cardiovascular safety. A large nationwide study of more than 100,000 subjects found that the mortality and vascular risk of repaglinide monotherapy in patients with and without previous myocardial infarction did not statistically differ from MET.[47]

One study found that Mg ADP augments the inhibitory effect of repaglinide on potassium ATP channels on the beta cells and smooth muscle but not on myocardial cells. The authors suggested that this effect could explain the absence of cardiovascular side effects with repaglinide.[48]

Dosage

The dose of repaglinide and relation to food are presented in Table 2.

Repaglinide is exclusively metabolized in the liver to inactive metabolites and secreted in the bile. Approximately 8% is excreted in the urine.[45] Thus, if the liver function is normal, the risk of hypoglycaemia in CKD patients is reduced.

Repaglinide may be used in patients with chronic kidney disease, but the NKF advises starting with a 0.5 mg does before each meal in patients with a GFR $\leq$30 ml/min/1.73 m^2 and gradually increasing the dose.[37]

Thiazolidinediones

Glucose tolerance was reportedly improved in diabetic patients on clofibrate as early as 1963.[49] This finding lead to the discovery of ciglitazone, the first drug of this group of medications in Japan in 1970s. However, ciglitazone was not marketed due to side effects in animals.[50] Troglitazone was introduced in the U.S.A. in 1997 followed by the approval of rosiglitazone and pioglitazone in 1999.

Troglitazone was withdrawn in 2000 because it was associated with hepatic toxicity.[51]

Mechanism of action and efficacy

Thiazolidinediones are agonists of peroxisome proliferation-activated receptor gamma (PPARγ), which is a determinant of insulin sensitivity.[50] Thus, thiazolidinediones increase glucose uptake by skeletal muscles and adipose tissue and suppress hepatic gluconeogenesis.[52]

Thiazolidinediones are effective in reducing blood glucose. In a systematic review of nine controlled trials of pioglitazone monotherapy versus control, thiazolidinediones reduced HbA1C with a WMAD of 0.97 (95% CI −1.18 to 0.75).[10] The corresponding figures for eight controlled trials of rosiglitazone versus control were −1.16 (−1.39 to 0.92). Pioglitazone monotherapy reduced HbA1C by 1–1.6% compared with placebo in a randomized trial.[53]

An addition study of rosiglitazone versus placebo for 24 weeks revealed a reduction of mean HbA1C of 1.2 and 1.5% for doses of 2 and 4 mg twice daily, respectively.[54] This class may require approximately 3 months to achieve its maximum effect.[55] Thus, HbA1C measurement is not reliable during this initial period.

The durability of the effect in monotherapy was 85% at 5 years, which is better than that of MET and of SU.[12] One of the advantages of this class is that they do not tend to produce hypoglycaemia when administered as monotherapy.

Side effects and contraindications

One of the major side effects of TZDs is weight gain. Over 5 years, the average weight gain with rosiglitazone was 4.9 kg, whereas glibenclamide caused a weight gain of 1.6 kg in the first year and stabilized thereafter.[12] In the same study, metformin produced a weight loss of 2.9 kg in the 5 years.

The weight gain associated with TZDs is partly due to oedema and fat. However, the increase in fat involves subcutaneous fat more often than visceral fat.[56] The oedema is dose-dependent and is worst in combination with insulin.[57] The oedema is refractory to loop diuretics but may respond to spironolactone or hydrochlorothiazide treatment.[58]

This class should be avoided in the presence of heart failure and liver disease.[11] Liver function should be assessed before starting these patients on this treatment and periodically thereafter.[11,59,60] TZD side effects are summarized in Table 1.

Cardiovascular safety

The concern about heart failure was noted prior to TZD marketing given that the premarketing trials excluded patients with class III and IV heart disease.[61]

Congestive heart failure occurs in less than 1% of patients on rosiglitazone monotherapy but increases to 2% and 3% upon the addition of 4 mg and 8 mg daily, respectively, with comparable data for pioglitazone.[61]

The American Heart Association/American Diabetes Association issued consensus statement regarding the use of TZD and heart failure in 2003, urging clinicians to evaluate heart disease patients prior to starting TZD and afterwards if oedema develops. If the patient experiences heart failure, treatment should be stopped.[59–61]

In June 2007, a meta-analysis of 42 trials concluded that patients treated with rosiglitazone had a significant increase in myocardial infarction (odds ratio = 1.43 (95% CI 1.03–1.98)) compared with controls, with insignificant increase in cardiovascular mortality.[62] This report spread panic across the medical community. Before this report, the FDA was ready to license the antidiabetic drug muraglitazar. However, approval was declined after an independent analysis revealed that the drug caused increased mortality and major cardiovascular morbidity.[63]

In 2008, the FDA terminated a trial of intensive treatment in diabetic patients with high cardiovascular risk aiming at normalizing HbA1C after discovering that the intensive arm exhibited increased mortality.[64] After the preceding three reports, the FDA revised the licensing process of diabetes medications to include adequate cardiovascular studies before and after licensing.[27]

In 2009, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial reported an increase in heart failure when rosiglitazone was added to MET or SU compared with a combination of MET and SU, but cardiovascular mortality was not increased.[65] A further re-evaluation of this trial as required by the FDA with 328 additional person-years reported similar results.[66]

Rosiglitazone was banned in Europe in 2010. The FDA issued certain restrictions on its use. However, the restrictions were lifted in November 2013 after re-evaluation of cardiovascular outcomes in the RECORD trial and obtaining additional evidence that reduced their concern.[66] However, the FDA continues to have uncertainties.[67]

Pioglitazone may be different regarding myocardial infarction. Pioglitazone reduces fatal and non-fatal myocardial infarction in patients with T2DM and previous myocardial infarction,[68] and a meta-analysis demonstrated that pioglitazone significantly reduced the risk of stroke, myocardial infarction and death while increasing serious heart failure.[69]

Both rosiglitazone and pioglitazone increase the risk of upper and lower limb fractures, especially in women, and reduce bone mineral density.[70,71]

Pioglitazone increases the risk of bladder cancer[68,72] and was banned in Japan, India, Australia and Canada. However, a recent study of a large cohort of 207,714 patients, including 23,548 who used pioglitazone, failed to demonstrate a significant association between pioglitazone use and the risk of bladder cancer.[73]

Dosage

The doses of pioglitazone and rosiglitazone and relation to food consumption are presented in Table 2.

The NKF does not advise any change in the dose of TZDs in patients with CKD.[37] However, one must be careful if these patients are oedematous as these drugs may worsen the oedema, and these patients should be assessed for heart failure.

Alpha-glucosidase inhibitors

The first member of this group is acarbose, which was approved by the FDA in 1995.

Mechanism of action and efficacy

Acarbose inhibits alpha-glucosidases at the intestinal brush border.[11] This process reduces carbohydrate absorption and postprandial blood glucose. These drugs exert a modest effect on diabetes control as a monotherapy. In a meta-analysis of 28 trials, acarbose reduced HbA1C by 0.77% versus controls.[10] In the UKPDS trial over a 3-year period, acarbose reduced the median HbA1C by 0.5 compared with controls. However, only 39% of patients completed the 3-year study on acarbose due to side effects.[74] In a Cochrane systematic review of 41 trials, acarbose reduced HbA1C by 0.8% compared with placebo, but most of the studies lasted only 24 weeks.[75]

The advantages of acarbose include being weight neutral and the lack of hypoglycaemia. Acarbose acts at the level of small intestine and does not have many systemic effects. It appears to be more effective when the patient's diet contains large amounts of complex carbohydrates. A systematic meta-analysis reported that acarbose was more effective in patients on an Eastern diet (contains complex carbohydrates) compared with those on a Western diet (contains processed meats and refined carbohydrates).[76]

In an open study, the hypoglycaemic effect of acarbose as monotherapy or in combination was sustained up to 5 years.[77]

Side effects and contraindications

The main side effects of acarbose are GI, such as abdominal pain, bloating, flatulence, and diarrhoea, which occur at different frequencies in different populations.[11]

In one study, the side effects occurred in 50% of patients during the initial 4-week period and were only noted 13.8% of patients during the last 4 weeks of a 24-week study.[78]

These GI side effects are dose-dependent.[75] However, these side effects may be quite troublesome in some populations. In the UKPDS, 61% of the patients left the 3-year study due to side effects.[74] However, the drug appears to be more tolerable in the East, with 2.03% of patients experiencing side effects in a study involving patients from the Far East, Middle East, Morocco and Poland.[79]

In a recent analysis of post-marketing data on more than 67,000 patients from 21 Asian and Caucasian countries, GI side effects were present in 2.76% of patients, and acarbose was only slightly more effective in South East and East Asians.[80] In this report, abnormal liver function tests, which were reported in early trials, were observed in only 0.11% of patients.

Acarbose is contraindicated in liver cirrhosis and inflammatory bowel disease.[81] The side effects of acarbose are summarized in Table 1.

Cardiovascular safety

We are not aware of large-scale controlled results reporting the effect of acarbose on cardiovascular morbidity

and mortality over a long period, but the use of acarbose to prevent T2DM in subjects with impaired glucose tolerance was associated with a reduction of silent myocardial infarction.[82] However, this result was noted in a sub-study analysis of only 1181 patients. Moreover, the risk of cardiovascular disease in pre-diabetes patients is not similar to that of patients with T2DM who develop abnormal coronary arteries many years prior to the diagnosis of T2DM.

Dosage

The dose of acarbose and relation to food consumption are summarized in Table 2. To reduce GI side effects, it is advisable to start with 25 mg administered before each meal. The dose is then increased to 50 mg and then 100 mg after 4–8 weeks as needed and tolerated. Importantly, doses greater than 50 mg for patients who weigh >60 kg reduce the risk of increasing liver enzymes.[81]

Although acarbose is mainly metabolized by bacteria in the intestinal tract and digestive enzymes, approximately one-third of the dose may be absorbed and appears in the urine.[83] Thus, one must be careful when administered to patients with renal impairment. The National Kidney Foundation (NKF) advise avoiding acarbose if the GFR is <30 ml/min/1.73 m^2.[37,81]

Dipeptidyl peptidase-4 inhibitors

These compounds are based on the incretin effect in which insulin secretion is modulated by a substance released from the intestine into the circulation in response to food ingestion. In 1964, McIntyre and other researchers reported the first proof that oral glucose induces more insulin secretion than IV glucose based on alimentary mechanisms.[84] Two incretins are well characterized: the glucose-dependent insulinotropic polypeptide (GIP) and the more potent GLP-1. Both drugs exhibit glucose-dependent insulin stimulation.[85] GLP-1 inhibits glucagon secretion, delays gastric emptying, and decreases appetite, causing weight loss in addition to glucose-dependent insulin secretion. However, GLP-1 is degraded rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4). Several inhibitors of this enzyme (DPP-4I) have been synthesized. The first inhibitor, sitagliptin, was approved by the FDA in 2006. Other inhibitors marketed in KSA include vildagliptin, saxagliptin, and linagliptin.

Mechanism of action and efficacy

These agents modestly increase GLP-1 in the physiological range. Thus, their effect on glucose reduction and weight are not as notable as GLP-1 agonists. These agents do not affect gastric emptying.[86] These drugs induce glucose-dependent insulin secretion in the first and second phases, inhibit glucagon secretion and suppress hepatic gluconeogenesis.[87] These agents rarely produce hypoglycaemia in monotherapy and exhibit a weight-neural effect.[88]

In a systematic review, DPP-4I reduced HbA1C compared with placebo with a WMD of −0.74 (95% CI −0.85 to −0.62).[89] Compared with MET as monotherapy, these agents exhibited less reduction in HbA1C with WMD of 0.20 (95% CI 0.08–0.32).[90]

The durability of DPP-4I was reported in an observational study of sitagliptin in combination with MET in which patients had a median of 43.2 months before requiring a treatment change which was more than double the period required by the combination of SU with MET.[91] In another study assessing sitagliptin in combination with MET, 72.2% of patients responded after 1 year, and the response rate was reduced to 35.4% at 4 years.[92]

This class of drugs is not recommended as the first-line monotherapy. However, these drugs may be used in a manner similar to other second-line agents if MET is contraindicated or not tolerated.[7]

Side effects and contraindications

This class may produce allergic reactions as serious as angioedema and anaphylaxis.[93] Similarly, pancreatitis has been rarely reported, and patients should be warned to contact their physician immediately if they exhibit continuous severe abdominal pain, which may radiate to the back.[94] Although a 5-year study of greater than 20,000 new users of incretins reported no increase in pancreatitis compared with SU users,[95] no large long-term controlled studies have abolished the association with pancreatitis. Vildagliptin may be associated with an increase in the liver enzymes and is contraindicated in liver impairment. Transaminases should be assessed prior to administer this drug, and assessments should be repeated every 3 months during the first year.[96]

Severe disabling arthralgia has been observed in this group, and the FDA added a warning about this complication in August 2015.[97] The side effects of DPP-4I are summarized in Table 1.

Cardiovascular safety

The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with DM–TIMI53 (SAVOR-TIME) study was a large study that recruited 16,492 patients with or at risk of cardiovascular disease who were randomized to receive saxagliptin or placebo and followed up for a median of 2.1 years. The study reported a significant increase in the rate of admissions for heart failure in the saxagliptin group compared with placebo with a hazards ratio of 1.27 (95% CI 1.07–1.51).[98] Although this study revealed no increase in ischaemic events, it raised concerns about cardiovascular safety.

A network meta-analysis of 10 randomized trials including 2967 patients found no significant difference between patients taking DPP-4I and placebo with regards to mortality or cardiovascular disease.[99] A recent observational study of greater than 10,000 matched pairs on DPP-4I added to MET and those on SU added to MET reported a reduced risk of all-cause mortality and ischaemic stroke with DPP-4I. However, concern regarding the cardiovascular safety of SU has been noted for a long time. Moreover, DPP-4I did not reduce myocardial infarction or admission for heart failure compared with SU.[100]

The FDA conducted an on-treatment analysis of deaths in patients on saxagliptin in SAVOR-TIME, and their results suggest a significant or near significant increase in all-cause

mortality. In April 2015, the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA voted that saxagliptin labelling should include the potential increase in heart failure, all-cause mortality, pancreatitis and impaired renal function.[101]

The cardiovascular safety of DPP-4I has not been demonstrated.

Dosage

The dose of DPP-4I and its relation to food intake are presented in Table 2. In April 2015, the Endocrinologic and Metabolic Drugs Advisory Committee discussed the (SAVOR-TIMI) trials and commented on the observed reduction in eGFR and improved albumin to creatinine ration with saxagliptin with a low level of concerns. The Committee considered these effects as a potential signal that requires further study.[101] The NKF recommends the following dose adjustment in patients with CKD.[37]

Sitagliptin: Dose to be reduced to 50 mg daily if GFR is 30–50 ml/min/1.73 m^2 or 25 mg if GFR <30.

Saxagliptin: reduce the daily dose to 2.5 mg if GFR is ≤50 ml/min/1.73 m^2.

Vildagliptin: reduce the daily dose to 50 mg if GFR is <50 ml/min/1.73 m^2.

It is advisable to assess renal function prior to initiating the above three medications and periodically thereafter. No dose adjustment is needed for linagliptin.

Sodium–glucose cotransporter-2 inhibitors

The kidney plays an important role in glucose homeostasis via the enzyme sodium–glucose cotransporter-2 (SGLT2), which reabsorbs sodium and glucose in the proximal renal tubules. This enzyme may absorb approximately 90% of the 180 g of glucose filtered daily.[102] Potent inhibitors of this enzyme have been developed (SGLT2I).

Dapagliflozin was the first member of this group, which was approved in Europe in 2012. Dapagliflozin was not approved by the FDA initially due to concerns regarding the risk of breast and bladder cancer. However, the drug was approved in 2014 following more safety data.[103] Canagliflozin was approved by the FDA in 2013. Empagliflozin was approved in 2014. This group is new discovered, and we are learning more about its efficacy and side effects.

Mechanism of action and efficacy

These agents reduce blood glucose via a non-insulin-dependent mechanism, namely glycosuria. Glycosuria is accompanied by osmotic diuresis.

In addition to their inhibition of glucose reabsorption, which aids in reducing blood glucose, glycosuria may result in a loss of approximately 300 k/calories per day, which aids in weight loss and improves insulin sensitivity.[103]

These agents induced significant reductions in HbA1C compared with placebo, with a WMD of −0.66% (95% CI −0.73 to −0.58), and weight, with WMD of −1.7 kg (95% CI −2.0 to −1.5).[104] Compared with MET, sitagliptin and SU, no significant difference in HbA1C was noted, but these agents produced significant weight reduction with a mean difference of −1.8 kg (95% CI −3.5 to −0.11). Due to their recent introduction, no data on long-term durability are available. A meta-analysis reported that these agents reduced HbA1C compared with placebo with a WMD of −0.49% for 1 year and −0.503% for 2 years. These agents also reduced weight significantly with corresponding values at 1 and 2 years of −2.47 kg and −2.990 kg, respectively.[105]

Side effects and contraindications

The polyuria resulting from extra glucose in the urine may produce dehydration with postural hypotension, especially in the elderly and patients on diuretics. This effect may be of particular concern in our hot countries during the summer time.[103]

Glycosuria predisposes patients to urinary and genital tract infections, especially females. At 2 years of treatment, SGLT2I increased the risk of urinary tract and genital tract infections with an odds ratio of 1.477 and 4.196, respectively.[105] Although these infections are cleared via simple treatment,[106] it is advisable to avoid using these agents in patients with preceding recurrent urinary tract infections.

These results may produce a slight reduction of GFR. GFR was reduced by 10.8%[107] in patients on dapagliflozin, but this condition is typically corrected in a short period of time. The FDA drug labels advise assessing creatinine prior to starting SGLT2I and periodically thereafter.[108,109]

Hyperkalaemia may develop after starting canagliflozin, and serum potassium should be assessed before and periodically after administration, especially in predisposed patients, such as those on spironolactone or ACE inhibitors.[109] The FDA has issued a safety podcast drawing attention to the increase in bone fractures and decrease in bone mineral density that may be associated with these medications.[110]

Cases of euglycaemic diabetic ketoacidosis have been reported with the use of SGLT2I.[111] The majority of cases exhibited type 1 diabetes mellitus or occurred with off-label use in combination with insulin. It is advisable to evaluate any patient on these medications for ketoacidosis if they experience nausea and vomiting or malaise. The side effects of SGLT-2I are summarized in Table 1.

Cardiovascular safety

A meta-analysis of 14 dapagliflozin trials reported an odds ratio for cardiovascular outcomes of 0.73 (95% CI 0.46–1.16) compared with controls.[104] The same study reported that canagliflozin cardiovascular outcomes were observed with an odds ratio of 0.95 (95% CI 0.71–1.26) compared with placebo or active comparators. In a study of more than 7000 diabetic patients with high cardiovascular risk followed for a median of 3.1 years, empagliflozin significantly reduced death from cardiovascular causes and admission for heart failure.[112] Although these reports appear promising, reassuring large, long-term controlled trials are not available. Moreover, evidence suggests that SGLT1 cardiac expression increases 2- to 3-fold in patients with diabetes and cardiac ischaemia. This effect may facilitate glucose entry into myocytes. As the

effect of SGLT2I on SGLT1 varies widely, one cannot guarantee that this inhibition will not be detrimental to the heart under the above conditions.[113]

Dosage

Dapagliflozin is started at 5 mg daily without regards to food. The maximum daily dose is 10 mg.[108] The starting dose of canagliflozin is 100 mg before the first meal, and the dose may be increased as tolerated up to 300 mg daily.[109] Empagliflozin is started as 10 mg in the morning, and the dose may be increased to 25 mg if tolerated.[114]

Dapagliflozin should not be prescribed if the eGFR is <60 ml/min/1.73 m^2.[108] Canagliflozin should not be prescribed if the eGFR is <45 ml/min/1.73 m^2.[109] The canagliflozin dose should not be greater than 100 mg if the eGFR is 45 to less than 60 ml/min/1.73 m^2.[97] Empagliflozin should not be used if the eGFR is less than 45 ml/min/1.73 m^2, and no dose adjustment is needed at or above this eGFR.[114]

Judicious use of oral hypoglycaemic agents

There are many important factors that must be considered before making the therapeutic plan. These factors include the following:

1. Degree of hyperglycaemia and the level of HbA1C: If HbA1C is <7.5%, MET is the initial drug of choice (unless contraindicated) in addition to life-style modification.[7,115] When HbA1C is higher, the treatment becomes more complex, but MET remains the basic drug to which other medications are added. The AACE/ACE advises dual therapy if entry HbA1C is ≥7.5%.
   However the American Diabetes Association/European Association for the Study of Diabetes (ADA/EUASD) advises dual therapy when the HbA1C is ≥9%.[7,115] Dual therapy appears sensible when the entry HbA1C is ≥7.5% as MET is slightly less effective in controlling the fasting blood glucose during the initial six months.[116] The early initiation of dual therapy is facilitated by the availability of many oral agents with similar efficacies and low risks of hypoglycaemia.
   Triple therapy may be administered if dual therapy fails to achieve the desirable control. Insulin is added to other agents if the entry HbA1C is >9% with symptoms of hyperglycaemia according to the AACE/ACE guidelines, whereas ADA/EASD guidelines recommend initiating combination with insulin injectable therapy when blood glucose is ≥300 mg/dl (16.7 mmol/L) and/or HbA1C ≥10−12%. In such patients, treatment is simplified as the glucose toxicity clears. The possibility of achieving an HbA1C of less than 6.5% in a symptomatic patient with an HbA1C of >9% by dual oral therapy is small.[34] A third drug is likely to contribute less than it would do in mono- or dual therapy.[117]
   Both guidelines advise moving from one stage to the next if the target A1C is not achieved within 3 months. Basal insulin, GLP-1 receptor agonists, SU, DPPI, TZD, and SGLT2I may be used with MET in dual therapy, keeping in mind comorbidities that may preclude the use of one class, e.g., TZD and DPPI should be avoided in patients with heart failure.
2. Patient age and diabetes duration: In a young patient with newly diagnosed diabetes with no comorbidities, one aims for an HbA1C of <6.5%, and all needed combinations are used. In a fragile old patient with long standing diabetes with vascular complications and chronic illnesses, the target HbA1C may be <8% or even <8.5%.[7]
3. Side effects of medications: The most important side effect is hypoglycaemia. The AACE/ACE guidelines advise caution when using SU or GLN across the 3 steps of intensifying oral medications and consider both classes to be the least favourable due to potential hypoglycaemia.[115] Glinides may be used instead of SU in patients with unpredictable food intake or those who develop late postprandial hypoglycaemia with (SU).[7]
   Another important side effect to consider is weight gain. Weight gain is more often observed with SU and with TZD, and the combination is not favourable in obese patients.
4. Cost of medication: The target HbA1C was achieved in the UKPDS with inexpensive medications, such as MET, SU or insulin. Moreover, MET and SU are superior or at least non-inferior to other expensive medications, have been used for longer periods of time,[10] and are available in cheap generic formulae. If hypoglycaemia can be prevented, this combination seems appropriate in our developing countries. Table 2 presents the monthly cost of different antihyperglycaemic agents.
5. Efficacy in reducing HbA1C: Most oral hypoglycaemic agents reduce HbA1C by 1 absolute percentage point in monotherapy. Dual therapy offers a greater reduction in HbA1C of approximately 1 absolute percentage point compared with monotherapy.[10] As SU reduce HbA1C compared with controls by a weighted mean absolute difference of −1.52%,[10] these drugs may be appropriate in a young patient with moderately high glucose. In these patients, TZDs may not be an appropriate starter as they take several weeks to exert their full effects.[55]
   The use of SU is most appropriate for patients with T2DM with an onset within 5 years and no end-organ involvement who are keen on adopting healthy lifestyle with frequent blood glucose monitoring to reduce hypoglycaemia and weight gain.[115] SGLT2Is are considered 2nd or 3rd line agents, and they may be used for insulin sparing in T2DM patients on large doses of insulin.[7]

Guidelines now advise individualizing the treatment according to all of the features of the case and taking into consideration the preference of the patient. One should not forget that insulin (basal) is a therapeutic option to add to these medications in all of the stages after monotherapy.

It is important to stress here the importance of avoiding threatening the patients that insulin injections will be added if they do not adhere to diet and exercise for control. I have witnessed physicians making this threat, which preconditions the patients against insulin use when needed.

Fixed drug combinations

Some companies produce formulae that contain MET in addition to another medication. These drugs have been

suggested to encourage patient compliance as a result of reduced pill burden. The bioavailability, tolerability and efficacy of these combinations were similar to the individual components in dual therapy.[118] Patients who switched from dual therapy to fixed combination had a 12.4% increase in adherence to medication.[119] One of their major limitations involves the lack of flexibility of the dose. In some combinations, metformin is available in an extended release formula. In other combination, it is available as an immediate release formula, which may not be tolerated by some patients.[120]

Conclusion

We now have a variety of antihyperglycaemic agents with different mechanisms of action. Their use should be individualized according to the health status and preference of the patient, keeping in mind their efficacy and side effects. Metformin remains the drug of choice in monotherapy, and the others are added to it. However, SUs are becoming less favourable as they may produce hypoglycaemia. Cardiovascular risk has received more attention and should be investigated thoroughly before licensing newer agents.

Conflict of interest

The author has no conflict of interest to declare.

Authors' contributions

MSA is the sole author of this article. He is responsible for the design, interpretation of data for the work, drafting, revising it critically and approving the final version. He is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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