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REVIEW

Safety and Efficacy of Sitagliptin-Metformin in Fixed Combination for the Treatment of Type 2 Diabetes Mellitus

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Abstract: The biguanide, metformin, is considered first-line treatment for type 2 diabetes. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor acts through the incretin pathway and has a glucose dependent mode of action. The complementary hypoglycemic properties of these drugs make fixed dose combination treatment an attractive prospect. Evidence from recent clinical trials suggests a beneficial effect of the combination on efficacy, demonstrated by significant improvement of hemoglobin A_{1c} (HbA_{1c}), fasting and postprandial glucose levels. The fixed dose combination is likely to have greater patient tolerability compared with monotherapy with either agent because of low rates of hypoglycemia, weight neutrality, and lower rates of side effects. High acquisition cost and paucity of long-term safety data are, however, potential barriers to their wider use. An overview of the pharmacology and clinical outcomes from recent trials of the metformin-sitagliptin combination and how the combination could fit into the type 2 diabetes treatment algorithm is presented in this review.

Keywords: metformin, sitagliptin, DPP-4 inhibitors, incretin-based therapies, type 2 diabetes

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Introduction

Diabetes mellitus is a global epidemic, and type 2 diabetes accounts for almost 90% of patients with the disease. In many countries, almost 10% of the health care budget is allocated for type 2 diabetes care.[1] Type 2 diabetes is a condition in which defective insulin action and gradual loss of insulin secretion from pancreatic β cells leads to a state of hyperglycemia. The disease results from a combination of both environmental factors, including a sedentary life style and obesity and genetic predisposition. Good glycemic control alongside risk factor modification is central to preventing the microvascular complications of diabetes including retinopathy, nephropathy, and neuropathy.[2] Early initiation of pharmacological treatment following diagnosis has been recommended, and metformin is regarded as the drug of choice for initial treatment.[3] However, metformin alongside other antihyperglycemic treatments has not been able to alter the progressive nature of type 2 diabetes. Additionally, a recent position statement from American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) have recommended initiating patients with hemoglobin A_{1c} (HbA_{1c}) > 9% on combination treatment.[4] Several trials have demonstrated that the combination of different agents in the treatment of type 2 diabetes has been more efficacious and is better tolerated than high doses of individual drugs.[5–7] Combination therapies in the form of fixed dose combinations also makes dosing convenient and improves patient compliance. Fixed dose combinations (FDC) of sitagliptin and metformin are available as 50 mg/500 mg and 50 mg/1000 mg tablets and are usually taken twice daily with meals. In this review, the evidence behind the efficacy and safety of the FDC from recent clinical trials and some earlier trials in which the individual tablets were used together as a dual therapy is discussed.

Mechanism of Action

Sitagliptin

Sitagliptin is a potent, oral, selective dipeptidyl peptidase-4 (DPP-4) inhibitor and produces its effect by increasing the concentration of endogenous incretin hormones, which in turn stimulate insulin secretion from β cells in a glucose dependent manner. The incretin hormones are released from the gut following the ingestion of nutrients.[8] Two of the major incretin hormones are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which are released from the enteroendocrine L cells and K cells in the duodenum and jejunum. GLP-1, in particular, plays an important role in glucose control by increasing insulin secretion from β cells and decreasing glucagon secretion from α cells in a glucose dependent manner. In addition to effects on pancreatic islets, GLP-1 contributes to glucose homeostasis by regulating gastric emptying, delaying nutrient absorption, and prolonging postprandial satiety.[9] There are also numerous extrapancreatic effects of GLP-1 and the other incretin hormones.[10]

The half-life of endogenous GLP-1 is around 2 minutes, as it is rapidly degraded by the enzyme DPP-4. DPP-4 is a protease enzyme bound to the cell membrane of most organs including kidney, intestine, bone marrow, liver, pancreas, placenta, thymus, spleen, vascular endothelium, and lymphoid and myeloid cells. There is also a smaller soluble circulating form of the enzyme. Both forms cleave the terminal amino acid alanine of GLP-1 and GIP at position 2, rendering them inactive leading to degradation.[11] The enzymatic activity of DPP-4 is a major determinant of the biological activity of GLP-1, and more than 75% of GLP-1 produced in the gut is degraded before leaving the intestine. The liver degrades a further 40% to 50% of the remaining GLP-1, and only 10% to 15% of secreted GLP-1 reaches the systemic circulation in the active form.[12–14] Inhibition of DPP-4 in the capillaries of the lamina propria can prevent enzymic degradation and in healthy adults has been found to increase fasting and postmeal plasma GLP-1 levels.[15]

There are 2 ways in which the incretin pathway can be mobilized for the treatment of hyperglycemia in people with type 2 diabetes: first, by using incretin mimetics or GLP-1 receptor agonists resistant to degradation by DPP-4 (examples include exenatide, lixisenatide, and liraglutide); and second, by using DPP-4 inhibitors, which increase the plasma half-life of endogenous GLP-1 (examples include sitagliptin, vildagliptin, saxagliptin, and linagliptin).[16,17] It follows that the efficacy of DPP-4 inhibitors maybe dependent on the secretion of endogenous GLP-1. It has been reported that GLP-1 secretion is reduced in type 2 diabetes, with reduced fasting and postprandial levels.[18–20] However, more recent studies have not supported this observation.[21] Moreover, in a

recent meta-analysis, Nauck et al analyzed data from 9 studies and 406 participants comparing integrated responses of total GLP-1 with oral glucose or standard mixed meal between people with type 2 diabetes and weight-matched nondiabetic controls and did not find any significant difference between the 2 groups.[22] That said, incretin-based therapies including DPP-4 inhibitors are now being successfully used to improve blood glucose control in people with type 2 diabetes.

Metformin

Metformin is a synthetic biguanide and is the most widely prescribed medication for type 2 diabetes. Metformin accumulates within the mitochondria of cells, reducing adenosine triphosphate (ATP) production and activates AMP-activated protein kinase (AMPK). The downstream effect of AMPK activation in the liver is reduced gluconeogenesis and in skeletal muscle, upregulation of glucose transporters such as clucose transporter 4 (GLUT 4) leading to increased insulin-mediated glucose uptake.[23,24] Metformin also increases insulin receptor expression and tyrosine kinase activity, further enhancing insulin sensitivity of peripheral organs.[25] Reduced hepatic glucose production and increased glucose uptake in skeletal muscle reduces the fasting blood glucose level. It is also mildly anorexigenic and appears weight neutral.

Metformin improves postprandial blood glucose levels, which may in part be mediated through the incretin pathway. In obese, nondiabetic subjects, metformin has been found to increase plasma GLP-1 levels at 30 and 60 minutes after oral glucose.[26] In rodent studies, metformin has been found to increase plasma GLP-1 levels in a dose-dependent manner even in DPP-4 deficient rats, indicating that the effect of metformin on GLP-1 is independent of DPP-4 inhibition.[27] The mechanisms by which GLP-1 levels are increased by treatment with a combination of DPP-4 inhibitors, such as sitagliptin and metformin, might, therefore, be expected to be complementary.

Pharmacokinetic and Pharmacodynamic Profile and Adverse Drug Reactions

Sitagliptin

Sitagliptin is well absorbed orally and has a bioavailability of 87%.[28] There is dose dependent inhibition of DPP-4 activity, and almost 80% of enzyme activity is inhibited for 24 hours at 100 mg.[29,30] Maximum DPP-4 inhibition is noticed at 100 mg/day dosing, with no additional suppression at 200 mg/day.[31] Sitagliptin has minimal effects on cytochrome P450 enzymes and hence does not appear to have any clinically significant interactions with other medications.[30] Sitagliptin undergoes marginal metabolism in the body and is excreted in the urine by active tubular secretion. Renal function should be monitored during treatment and the dose reduced in modest or severe renal insufficiency, with 50 mg for patients with creatinine clearance of 30 to 50 mL/minute and 25 mg for creatinine clearance $<$30 mL/minute.[32] Sitagliptin is overall well tolerated. However, in a Cochrane review, a significant increase in all cause infections was described. There have been no reports of severe hypoglycemia with sitagliptin, although headache has been reported more frequently compared with placebo. Interestingly, the Cochrane review suggested that although sitagliptin was not found to cause weight gain, there was more weight loss with placebo treatment.[33]

Pancreatitis has been reported to be increased in patients taking sitagliptin. However, a causal relationship between sitagliptin and pancreatitis has not been established.[34] In a recent large population-based case-control study of type 2 diabetes, the use of incretin-based therapies, including sitagliptin, was reported to be associated with an increased rate of hospitalization secondary to acute pancreatitis. Although a statistical adjustment was made for potential confounders, the groups of incretin therapy users and nonusers were poorly matched.[35] A further concern related to incretin-based therapies is that of premalignant changes in pancreas tissue.[36] These data, which have been subject to some criticism, require validation.[37,38] A recent joint statement from the ADA/EASD/International Diabetes Federation (IDF) reported that there was insufficient evidence to change existing treatment recommendations and that patients currently on incretin-based therapies should continue to take them as prescribed by their health care professional.[39]

Finally, during the postmarketing surveillance of sitagliptin, allergic reactions including angioedema and exfoliative dermatological reactions such as Stevens-Johnsons syndrome were reported, typically within 3 months of starting treatment.[34] Other common

adverse effects reported are nasopharyngitis and upper respiratory tract infections.

Metformin

Metformin is administered orally, demonstrates 50% to 60% bioavailability, and its absorption is reduced and delayed with food. It has a half-life of approximately 6.2 hours and is usually administered 2 to 3 times a day. Almost 85% of the maximal glucose-lowering effect is seen at a dose of 500 mg 3 times daily, but patients may be prescribed up to 2000 mg/day.[40] Metformin is not significantly plasma protein bound and is not metabolized in the body. It is eliminated unchanged in urine by filtration and active tubular secretion, and dose reduction is recommended in renal impairment.[40] Lactic acidosis is a rare but potentially fatal complication of metformin treatment, mainly reported in patients with severe renal insufficiency and those given iodinated contrast medium.[41,42] Drug interactions have been reported with cimetidine, which increases metformin levels by 40% to 60%, by reducing its renal clearance.[43,44] There is also the possibility of interactions with cationic drugs such as digoxin and morphine, as they also undergo renal elimination by tubular secretion.[45] Usual side effects of metformin treatment are gastrointestinal, including nausea, vomiting, diarrhea, abdominal discomfort, and flatulence, which become tolerable over time and can be decreased by administering the drug with food.[42]

Fixed dose combination of sitagliptin and metformin

Metformin and sitagliptin have independent glucose lowering properties and may increase GLP-1 levels by working through complementary mechanisms. They also have few pharmacological interactions and a low risk of hypoglycemia, making coadministration an attractive therapeutic prospect. FDC tablets are available in doses of 50 mg sitagliptin + 500 mg metformin or 50 mg sitagliptin + 1000 mg metformin. In a randomized, open-label, 2-part, 2-period crossover study, bioequivalence between FDC and coadministration of corresponding doses of sitagliptin and metformin was established in 48 nondiabetic subjects supporting the efficacy and safety of fixed dose combination treatment.[46] In a placebo-controlled, multipledose, crossover trial in 13 patients with type 2 diabetes, steady state pharmacokinetics of sitagliptin and metformin were not altered by their coadministration, and no drug-related adverse effects were reported.[47] Currently, there are no trials comparing the effect of FDC of sitagliptin and metformin on patient compliance although it might be expected that treatment with an FDC could improve patient compliance compared with treatment with separate agents. Studies comparing patient compliance for FDC with separate coadministration of metformin and glyburide generally report improved treatment adherence when patients were changed from combination of free doses to FDC.[48,49] The product information for the FDC advises precaution against lactic acidosis for the metformin component and pancreatitis for the sitagliptin.[42]

Trials Assessing Efficacy and Safety of Metformin and Sitagliptin

Fixed dose combinations (FDCs)

There are 3 trials in which the FDC of sitagliptin and metformin was assessed (Table 1).

In the study by Reasner et al, FDC of sitagliptin/metformin (sita/met) 50/1000 mg twice daily was compared with metformin 1000 mg twice daily as the initial treatment in patients aged 18 to 78 years with type 2 diabetes for more than 3 years and a mean HbA_{1c} of 9.8%.[50] The primary end point was the effect of 18 weeks of treatment on mean HbA_{1c}, safety, and tolerability. In the study, 484 subjects in the sita/met FDC group and 482 patients in the metformin group completed the protocol. Reduction in HbA_{1c} was 2.4% (95% confidence interval [CI], −2.5 to −2.2) from baseline of 9.9% with sita/met FDC, which was significantly greater than the 1.8% (95% CI, −0.8 to −0.4) from baseline HbA_{1c} of 9.8% with metformin alone. This difference was consistent across all subgroups defined by age, gender, baseline body mass index (BMI), and duration of type 2 diabetes. Around 49% of patients on combination treatment achieved a target HbA_{1c} of $<7\%$ compared with 34% on metformin alone. Improvement in HbA_{1c} was greater in patients with a higher HbA_{1c} at baseline. There was also a greater reduction in fasting plasma glucose with the combination treatment (−3.8 mmol/L with combination and −3.0 mmol/L with metformin monotherapy). There was also a significant improvement in β-cell function, as measured by the homeostatic

Table 1. Efficacy and safety of sita/met fixed dose combination versus comparators.

Reference	Treatment (no. of participants)	Baseline HbA_{1c} In %	Change in HbA_{1c} In %	Other key efficacy end points	Hypoglycemia	Significant adverse events
Reasner et al[43]	Sita/Met 50/500 BD to Sita/Met 50/1000 BD (560) or	9.9	–2.4	Fasting glucose, Proinsulin/insulin ratio, HOMA-β, HOMA-IR, lipids	Sita/Met: 2.1% Met: 1.8%	AP: Sita/Met: 1.1%, Met: 3.9% D: Sita: 12%, Met: 16.6%
	Met 500 mg BD to Met 1000 mg BD (566)	9.8	–1.8			
Perez-Monteverde et al[44]	Phase A (12 weeks, 492)			Fasting glucose, post-prandial glucose, HOMA-β, lipids	Sita/Met: 2.3% Pio: 2.2%	Edema: Sita/Met: 0.9%, Pio: 6.1%
	Sita100 mg OD (244) or	9.0	–1			
	Pio 15 mg OD (248)	9.1	–0.9			
	Phase B (28 weeks, 455)					
	Sita/Met 50/1000 mg BD (224) or		–1.7			
	Pio 45 mg OD (231)		–1.4			
Wainstein et al[45]	Sita/Met 50/500 BD to Sita/Met 50/1000 BD (261) or	8.9	–1.9	Fasting glucose, post-prandial glucose, Fasting and post-prandial proinsulin/insulin, HOMA-β, HOMA-IR, QUICKI, lipids	Sita/Met: 8.4% Pio: 4.3%	D: Sita/Met: 25.3%, Pio: 4.3% N: Sita/Met: 4.6%, Pio: 1.2% V: Sita/Met: 1.9%, Pio: 0%
	Pio 30 mg OD to 45 mg OD (256)	8.9	–1.4			

Abbreviations: Sita, Sitagliptin; Met, Metformin; Pio, Pioglitazone; D, Diarrhea; N, Nausea; V, Vomiting; AP, Abdominal pain; OD, once daily; BD, twice daily.

model assessment β (HOMA-β), a surrogate marker of insulin secretion derived from simultaneous blood glucose and insulin levels, with sita/met FDC compared with metformin monotherapy. At week 18, body weight was reduced by 1.6 kg in both groups. Weight loss was progressive until 12 weeks with a plateau between 12 and 18 weeks. Both sita/met FDC and metformin resulted in small improvement in total cholesterol, HDL cholesterol, triglyceride, and non-HDL cholesterol, and the changes were comparable between groups.

The incidence of hypoglycemia was low and similar in the FDC and monotherapy groups. Overall, gastrointestinal side effects were observed in 20.6% of patients on FDC and 24.6% patients on monotherapy. Diarrhea was the most common gastrointestinal side effect reported, and the incidence was significantly lower in the FDC group. A similar trend was observed for abdominal pain.[50]

In the study by Perez-Monteverde et al, efficacy and safety of FDC of sita/met was compared with pioglitazone in patients who had moderate to severe hyperglycemia.[51] Patients aged 18 to 78 years, with inadequate glycemic control, HbA_{1c} of 7.5% to 12%, and drug naïve within the previous 3 months and not more than 4 weeks cumulatively in the previous 3 years, were randomized to receive for 12 weeks, either sita 100 mg daily or pioglitazone 15 mg daily, titrated up to 30 mg daily after 6 weeks. In the second phase of the trial, patients who had inadequate glycemic control at the end of 12 weeks were switched to sita/met 50/1000 mg FDC twice daily, if they were on sitagliptin and to pioglitazone 45 mg daily if they were on pioglitazone and studied up to week 40. The improvement in HbA_{1c} was comparable between sitagliptin –1.0% (95% CI, –1.2 to –0.9) from a baseline HbA_{1c} of 9% and with pioglitazone –0.9% (95% CI, –1.0 to –0.7) from a baseline HbA_{1c} of 9.1% at the end of 12 weeks of treatment. In both groups, greater benefit was observed in patients with a higher baseline HbA_{1c}. At the end of the second phase of the study, a significantly greater improvement in HbA_{1c} from baseline was observed in the 187 patients in the sita/met FDC group (–1.7%) compared with 200 patients in the pioglitazone group (–1.4%). Similarly, greater improvement was seen with the sita/met FDC for fasting plasma glucose (–2.5 mmol/L with sita/met FDC vs. –2.1 mmol/L with pioglitazone) and 2 hour postmeal glycemia (–5 mmol/L with sita/met FDC vs. –3.8 mmol/lL with pioglitazone). There was a significant improvement in β-cell function (HOMA-β) and proinsulin-insulin ratio with sita/met FDC compared

with pioglitazone. There was no change to total and LDL cholesterol in the sita/met FDC group, while an increase was reported with pioglitazone, resulting in a significant difference between groups. The change in triglyceride and HDL cholesterol was not different between groups.

At the end of week 40, although there were higher numbers of adverse events in the sita/met FDC group, this was not significantly different from the pioglitazone group. Gastrointestinal side effects including diarrhea, nausea, vomiting, and abdominal pain were not significantly different between treatment groups (9.5% with FDC of sita/met and 10.9% with pioglitazone). The incidence of edema was significantly higher with pioglitazone (0.9% with sita/met FDC and 6.1% with pioglitazone). Indeed, patients on pioglitazone gained 3.4 kg in body weight while patients on FDC of sita/met lost 1.1 kg. Symptomatic hypoglycemia was rare in both treatment groups, and severe hypoglycemia was not reported. Although biochemical adverse event occurrence of raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was seen in the sita/met FDC group, the change was only mild to moderate, and discontinuation or interruption of treatment was not necessary.

In the study by Wainstein et al, efficacy and safety of FDC of sita/met 50/1000 mg twice daily was compared with pioglitazone 45 mg per day after 32 weeks of treatment.[52] Studied were patients with type 2 diabetes between 18 and 78 years and HbA_{1c} of 7.5% to 12% who were not on any oral antidiabetics (OAD) in the 3 months prior to screening and not more than 4 weeks cumulatively in the previous 3 years. At the end of 32 weeks, the least squares mean change from baseline in HbA_{1c} was significantly lower in both treatment groups. In the 210 patients completing treatment (of 261 recruited) in the sita/met FDC group, HbA_{1c} improved by 1.9% (95% CI, −2.0 to −1.7) from a baseline HbA_{1c} of 8.9%, while in the 204 patients completing treatment (of 256 recruited) in the pioglitazone group, HbA_{1c} improved by 1.4% (95% CI, −1.5 to −1.3) from a baseline HbA_{1c} of 8.9%. In the population of patients with an $HbA_{1c} \geq 10\%$, there was significantly greater reduction of HbA_{1c} from baseline with sita/met FDC than with pioglitazone. The reduction of HbA_{1c} with sita/met FDC was more rapid than with pioglitazone. There was also more rapid and sustained reduction in fasting plasma glucose with maximal effect by 4 weeks with sita/met FDC (−3.1 mmol/L) compared with pioglitazone (−2.4 mmol/L). There was also a more significant improvement in the 2-hour postmeal glucose with sita/met FDC (−5.7 mmol/L) than with pioglitazone (−4.6 mmol/L). In the sita/met FDC group, there was a more significant decrease from baseline in the fasting pro-insulin/insulin ratio and increase from baseline in HOMA-β. However, there was greater reduction from baseline in insulin resistance measured as homeostasis model assessment-insulin resistance (HOMA-IR) and increase from baseline in insulin sensitivity, measured as quantitative insulin sensitivity check index (QUICKI) with pioglitazone. Unlike the previous trial, fasting total cholesterol, LDL cholesterol, and triglycerides were not changed from baseline with sita/met FDC but were reduced following treatment with pioglitazone.

There were numerically more adverse effects with sita/met FDC, mainly from a significantly higher incidence of gastrointestinal side effects including, diarrhea, nausea, vomiting, and abdominal pain/discomfort (25.6% with sita/met FDC and 14.3% with pioglitazone). The incidence of hypoglycemia, although numerically higher with sita/met FDC, was not statistically significant. Similar to the previous study, there was no report of severe hypoglycemia. A significantly higher rate of peripheral edema was seen in the pioglitazone group (7% with pioglitazone and 1.1% with sita/met FDC). Similar to the previous study, patients on pioglitazone gained 3.0 kg in body weight while those on sita/met FDC lost 1.4 kg. Patients on the FDC lost most of the weight in the first 8 weeks of treatment with a more gradual decline over the remainder of the treatment period. A mild increase in ALT levels was reported in 3 patients in the sita/met FDC group compared with none in the pioglitazone group. Of the 3 cases reported, ALT was >3 times upper limit of normal in 1 subject who was discontinued from the study, and levels settled within 7 days of stopping the study drug.

Dual therapy

In addition to the trials with sita/met FDC, there have been trials where coadministration of metformin and sitagliptin as dual therapy has been compared against either monotherapy with metformin or with

Table 2. Efficacy of dual therapy versus comparators.

Reference	Treatment (no. of participants)	Baseline HbA_{1c} In %	Change in HbA_{1c} In %	Other key efficacy end points	Hypoglycemia	Significant adverse events
Goldstein et al[46]	1. Sita: 50 + Met: 500 BD (183), or 2. Sita: 50 + Met 1000 BD (180), or 3. Sita: 100 OD (178), or 4. Met: 500 BD (179), or 5. Met: 1000 BD (179), or 6. PL: (169)	8.8 8.8 8.9 8.9 8.7 8.7	–1.4 –1.9 –0.66 –0.82 –1.13 0.17	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, lipids	1. 2.2% 2. 1.1% 3. 1.1% 4. 0.5% 5. 0.6% 6. 0.6%	1. GI: 24.7%* 2. GI: 17.9% 3. GI: 25.3% 4. GI: 15.9% 5. GI: 15.1% 6. GI: 10.8%
Williams-Herman et al[48] (50 week extension from 46, 47)	1. Sita: 50 + Met: 500 BD (101), or 2. Sita: 50 + Met 1000 BD (98), or 3. Sita: 100 OD (65), or 4. Met: 500 BD (80), or 5. Met: 1000 BD (95)		–1.4 –1.7 –1.2 –1.1 –1.3	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, lipids	1. 2.6% 2. 4.9% 3. 1.1% 4. 1.6% 5. 2.2%	1. GI: 29.5%* 2. GI: 33% 3. GI: 20.7% 4. GI: 20.9% 5. GI: 33%
Charbonnel et al[49]	1. Sita 100 + Met ≥ 1500 OD (464), or 2. Met ≥ 1500 + PL (237)	7.96 8.03	–0.67 –0.02	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, QUICKI	1. 1.3% 2. 2.1%	No significant difference including GI side effects
Raz et al[50]	1. Met ≥ 1500 + PL (94), or 2. Met ≥ 1500 + Sita 100 mg OD (96)	9.1 9.3	0 –1	Fasting glucose, Post-meal glucose, HOMA-β, HOMA-IR, QUICKI, lipids	1. 0% 2. 1%	No significant difference including GI side effects
Karasik et al[51]	Phase A (24 weeks) 1. Met ≥ 1500 + PL (237), or 2. Met ≥ 1500 + Sita 100 OD (464) Phase B (to 54 weeks) 1. Met + Sita 100 OD (for Sita, 391), or 2. Met + Glip up to 20 mg OD (for placebo, 164)	 8.0 8.0 7.9 7.9	 –0.7% –0.9%	Fasting glucose, lipids	Phase B 1. 1.7% 2. 13%	Change in body weight: 1. –0.9 Kg 2. +1.5 Kg AP: 1. 20% 2. 5.1%
Nauck et al[52]	1. Met ≥ 1500 + Sita 100 mg OD (386), or 2. Met ≥ 1500 + Glip up to 20 mg OD (412)	7.6 7.7	–0.51% –0.56%	Fasting glucose, proinsulin/insulin ratio, HOMA-β, HOMA-IR, QUICKI	1. 5% 2. 32%	Change in body weight: 1. –1.5 Kg 2. +1.1 Kg 1. F: 3.1% 2. F: 0.9% 1. Dizz: 3.7% 2. Dizz: 2.1%
Scott et al[53]	1. Met ≥ 1500 + Sita 100 mg OD (94), or 2. Met ≥ 1500 + Rosi 8 mg OD (87), or 3. Met > 1500 + PL (92) OD	7.8 7.7 7.7	–0.73 –0.79 –0.22	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, QUICKI, lipids	1. 1% 2. 1% 3. 2%	1. E: 1% 2. E: 5% 3. E: 1% 1. GI: 9% 2. GI: 7% 3. GI: 9%

(*Continued*)

Table 2. (*Continued*)

Reference	Treatment (no. of participants)	Baseline HbA_{1c} In %	Change in HbA_{1c} In %	Other key efficacy end points	Hypoglycemia	Significant adverse events
Scheen et al[54]	1. Met 1500–3000 + Sita 100 OD (374), or 2. Met 1500–3000 + Saxa 5 OD (365)	7.7 7.7	–0.62 –0.52	Fasting glucose, fasting insulin, C-peptide, glucagon, HOMA-2β	–	In both groups: Nasopharyngitis (4%), UTI (5.3%–5.7%), Influenza (5.7%–5.8%)
Bergenstal et al[55]	1. Met 1500–2000 + Exen 2/wk + PL (160), or 2. Met 1500–2000 + Sita 100 OD + PL (166), or 3. Met 1500–2000 + Pio 45 OD + PL (165)	8.6 8.5 8.5	–1.5 –0.9 –1.2	Fasting glucose, blood pressure, lipids, quality of life	1. 1% 2. 3% 3. 1%	Change in body weight: 1. –2.3 Kg 2. –0.8 Kg 3. +2.8 Kg 1. N/D: 24%/18% 2. N/D: 10%/10% 3. N/D: 5%/7% 4. E: 8%

Abbreviations: GI, Gastrointestinal—including abdominal pain, nausea, vomiting; PL, Placebo; AP, Abdominal pain; F, Fatigue; Dizz, Dizziness; E, Edema; N, Nausea; D, Diarrhea; Glip, Glipizide; Rosi, Rosiglitazone; Saxa, Saxagliptin; Exen, Exenatide; Pio, Pioglitazone.

metformin alongside another agent such as glipizide, rosiglitazone, saxagliptin, or exenatide (Table 2).

The trial by Goldstein et al was a double-blind placebo-controlled study of 1091 patients with type 2 diabetes for a mean duration of 4 years, aged 18–78 years, a mean HbA1C of 8.8% (range 6.3%–11.9%) with or without treatment with OADs.[53] Patients were randomized to receive 1 of 6 treatment regimens: sitagliptin 100 mg + metformin 1000 mg (sita100/met1000), or sitagliptin 100 mg + metformin 2000 mg (sita100/met2000), or metformin 1000 mg (met1000), or metformin 2000 mg (met2000), or sitagliptin 100 mg (sita100) or placebo daily for 24 weeks. Patients already on OADs were allowed a wash out period, while others were allowed direct entry after comparable run in periods. The efficacy of treatment, measured as placebo-adjusted reduction in HbA_{1c} (–1.4% in sita100/met1000, –1.9% in sita100/met2000) and proportion of patients achieving $HbA_{1c} < 7\%$ (66% in sita 100/met2000, 43% in sita100/met1000, 38% in met2000, 23% in met1000, 20% in sita100, and 9% in the placebo group) was significantly greater in the coadministration groups compared with respective monotherapy groups. Also the magnitude of response on HbA_{1c} with combination drugs was additive compared with the effects with each individual treatment. There was a significant improvement in fasting plasma glucose with coadministration compared with monotherapy. There was a significant improvement in β cell function, measured as HOMA-β and insulin resistance, measured as HOMA-IR with combination treatment.

The combination treatment was deemed safe, as the serious adverse events rate with combination treatment was comparable to placebo. The incidence of hypoglycemia was low and similar across all treatment groups. Gastrointestinal side effects including diarrhea, nausea, abdominal pain, and vomiting were related to the dose of metformin, both with monotherapy and coadministration. Loss of weight was observed in all treatment groups except monotherapy with sitagliptin.

Following the initial trial, an additional 885 patients (161 in sita100/met2000, 160 in sita100/met1000, 153 in met2000, 147 in met1000, and 141 in sita100) continued into a 30-week continuation period.[54] At the end of 54 weeks, least squares mean changes in HbA_{1c} from baseline were –1.8% in

sita100/met2000, −1.4% in sita100/met1000, −1.3% in met2000, −1.0% in met1000, and −0.8% in sita100. HbA_{1c} was substantially reduced with both low and high dose combination treatment at 54 weeks. Although the improvement in HbA_{1c} continued through 24 weeks, in most treatment groups, a nadir was seen at week 30. The improvement was greater for subjects with a higher baseline HbA_{1c}. Similar to the results at 24 weeks, improvement was seen at 54 weeks in fasting and postprandial glucose and HOMA-β, with larger improvement in coadministration groups. Weight was reduced in all treatment groups except sitagliptin monotherapy.

Five hundred and seventeen patients completed a further 50 week extension study.[55] At the end of 104 weeks the improvement in HbA_{1c} was preserved in all treatment groups (−1.7% in sita100/met2000, −1.4% in sita100/met1000, −1.3% in met2000, −1.1% in met1000 and −1.2% in sita100). The improvement with high dose coadministration was larger than monotherapy with either single agent. Both coadministration and monotherapy had similar adverse effect profile.

The trial by Charbonnel et al was a double-blind placebo-controlled study in which 701 patients aged 18 to 78 years with type 2 diabetes, mean duration of 6.2 years, with mild to moderate hyperglycemia (mean HbA_{1c} 8%, range 6.4%–11.0%) while taking metformin at 1500 mg/day were randomly assigned to receive sitagliptin 100 mg/day (464 patients) or placebo (237 patients) for 24 weeks. Patients on other OADs were changed over to metformin monotherapy with dose titration and eventually established on 1500 mg/day.[56] Sitagliptin was found to be more efficacious compared with placebo at the end of 24 weeks. There was an improvement in the primary end point, HbA_{1c} (−0.67%, −0.77% to −0.57%, P 0.001 from baseline) with sitagliptin compared with placebo. There was also a significant increase in patients achieving a $HbA_{1c} < 7\%$ (47% vs. 18.3%, $P < 0.001$) and a significant improvement in fasting plasma glucose (−1.4, −1.7 to −1.1, $P < 0.001$) from baseline with sitagliptin at 24 weeks. There was also a significant improvement in fasting insulin, fasting C-peptide, and β cell function measured as HOMA-β ($P < 0.001$). No significant effect was seen with sitagliptin on insulin resistance measured as HOMA-IR, although it resulted in a significant increase in the measure of insulin sensitivity (QUICKI). In the patients treated with sitagliptin, there was a significant decrease in plasma glucose, with an increase in C-peptide 2 hours after a standard meal. The study also investigated the effect of treatment on lipid profile. There was a statistically significant decrease in total cholesterol and triglycerides and increase in HDL cholesterol with sitagliptin compared with placebo while LDL cholesterol levels were unaffected. Rates of discontinuation of treatment for adverse effects and gastrointestinal side effects were similar in both groups. Some nonspecific side effects including nasopharyngitis, urinary tract infection, arthralgia, back pain, and cough were reported more commonly with sitagliptin, although the overall incidence was small. Weight loss was observed in both groups and not statistically significant between sitagliptin and placebo.

In the study by Raz et al, 159 patients with type 2 diabetes with HbA_{1c} between 8% and 11% were on metformin (≥1500 mg/day) for the first phase of the trial.[57] Patients who were compliant with a fasting plasma glucose between 7.2 and 15.5 mmol/L were randomized to receive, in addition to metformin, either sitagliptin 100 mg daily or placebo for 30 weeks. At 18 weeks, patients on sitagliptin had significantly lower HbA_{1c}, and they were more likely to achieve a $HbA_{1c} < 7\%$ at both 18 weeks and 30 weeks. Adverse events including hypoglycemia were similar between the 2 groups. Changes in body weight were similar in both groups.

There are some trials in which dual therapy with metformin and sitagliptin has been compared with other hypoglycaemic treatments. The trial by Karasik et al was a continuation of the trial by Charbonnel et al.[58] In the trial, 544 of the patients completing the initial study were recruited, and patients on placebo were switched to glipizide 5 mg daily and titrated to 15 mg daily for another 30 weeks.[58] Change in HbA_{1c} from baseline at the end of the trial was −0.7% with sitagliptin and −0.9% with glipizide. Hypoglycemia was more common with glipizide (16% against 1% with sitagliptin). Patients on sitagliptin lost 0.9 kg while patients on glipizide gained 1.5 kg in body weight.

Nauck et al performed a noninferiority trial comparing safety and efficacy of sitagliptin to glipizide when added to ongoing treatment with metformin (≥1,500 mg/day).[59] Seven hundred and thirty-nine

patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy with HbA_{1c} 6.5% to 10% were randomized to receive sitagliptin 100 mg daily or glipizide 5 mg daily titrated up to 20 mg daily. Improvement in HbA_{1c} at 54 weeks was comparable between the 2 groups (−0.51% with sitagliptin and −0.56% with glipizide). In all, 63% of patients on sitagliptin and 59% of patients on glipizide achieved $HbA_{1c} < 7\%$. There were more adverse events in patients on glipizide. Also patents on glipizide experienced more hypoglycemia (32% in patients on glipizide vs. 5% in patients on sitagliptin). Patients on sitagliptin lost 1.5 kg, while those on glipizide gained 1.1 kg in body weight. Sitaglitin was found to be noninferior to glipizide when added to metformin and, with respect to adverse effects, was better tolerated.

In the study by Scott et al, 273 patients on metformin (≥1500 mg/day) with a mean HbA_{1c} of 7.7% were randomized to receive sitagliptin 100 mg daily, rosiglitazone 8 mg daily, or placebo for 18 weeks.[60] At the end of 18 weeks changes in HbA_{1C} were −0.73% with sitagliptin and −0.79% for rosiglitazone and −0.22% with placebo and both changes were significant against placebo. Significantly more patients achieved a $HbA_{1c} < 7\%$ with sitagliptin (55%) compared with rosiglitazone (38%). Adverse effects, gastrointestinal side effects, and rates of hypoglycemia were comparable among the groups. Patients on sitagliptin and placebo lost 0.4 kg and 0.8 kg of body weight respectively, while there was a gain of 1.5 kg with rosiglitazone.

In the study by Scheen et al, patients with inadequate glycaemic control on stable doses of metformin (1500–3000 mg/day) were randomized to receive either sitagliptin 100 mg daily (n = 398) or saxagliptin 5 mg daily (n = 403) for 18 weeks.[61] Improvement of HbA_{1c} was achieved at 8 weeks and was maintained with both treatment groups throughout the study. Reduction in mean HbA_{1c} at 18 weeks was 0.62% with sitagliptin/metformin and 0.52% with saxagliptin/metformin. There was similar weight loss with both drugs. Class specific side effects of DPP-4 inhibitors including influenza, urinary tract infections, and nasopharyngitis were commonly reported adverse events. At the end of the trial, noninferiority was established between the 2 treatment arms.

The study by Bergenstal et al compared the efficacy and safety of exenatide (at 2 mg daily, n = 160), sitagliptin (at 100 mg daily, n = 166), and pioglitazone (45 mg once daily, n = 165) when added to stable doses of metformin for 26 weeks.[62] The largest reduction in HbA_{1c} from baseline was seen with exenatide (−1.5%), while the reduction with sitagliptin was 0.9%, and with pioglitazone, 1.2%. Also fasting plasma glucose was significantly improved with exenatide (−1.8 mmol/L) compared with sitagliptin (−0.9 mmol/L) but not when compared with pioglitazone (−1.5 mmol/L). Weight loss was most prominent with exenatide (−2.3 kg), which was significantly more compared with sitagliptin (−0.8 kg) and pioglitazone (2.8 kg). There were no reports of major hypoglycemia with any of the treatment arms.

Place in Therapy

Recently, a joint task force of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a position statement on management of hyperglycemia in type 2 diabetes that is less prescriptive than previous guidelines.[4] An important message is that treatment should be individualized to the needs of the patient. The ADA's standards of medical care in diabetes recommends lowering $HbA_{1c} < 7\%$ to reduce the incidence of microvascular disease and should be achieved by maintaining fasting and premeal blood glucose at <7.2 mmol/L and postprandial glucose at <10 mmol/L. A more stringent target of <6.5% is considered in selected patients (for example, those with short disease duration, long life expectancy, and no significant cardiovascular disease).[63] Following diagnosis, motivated patients with mild to moderate hyperglycemia ($HbA_{1c} < 7.5\%$) may be advised dietary and lifestyle changes for 3 to 6 months, prior to starting pharmacotherapy. The initial drug therapy of choice is metformin, unless it is not tolerated or is contraindicated. In patients presenting with a high HbA_{1c} (eg, >9%), where monotherapy is unlikely to achieve near normal target, the ADA/EASD position statement suggests that it is reasonable to start directly with a combination of 2 OADs.[4,64] Clearly in patients with significant hyperglycemia, insulin therapy should be considered from the outset. For patients on metformin alone in whom the HbA_{1c} target is not achieved after 3 months on monotherapy,

a second oral agent, GLP-1 receptor agonist or basal insulin, can be added, again with insulin being more appropriate for people with higher HbA_{1c} values. Uniform recommendations on the best agent to be used after or combined with metformin have not been made, largely because of the paucity of long-term comparative-effectiveness trials. Among the possible agents to add on to metformin, DPP-4 inhibitors are recognized as oral drugs with intermediate efficacy, with low risk of hypoglycemia, and have rarely been reported to have major side effects. They are weight neutral but have a cost that is higher than some of the older therapies.[4]

Although sulfonylureas have traditionally been the OAD of choice to add on to metformin and are highly effective with respect to glucose lowering, they are associated with modest weight gain and risk of hypoglycemia.[65,66] Moreover, they seem to have a higher secondary failure rate than other drugs.[67] While sulfonylureas are effective at glucose lowering, their side effects are well documented and they are cheaper than newer agents and their side effect profile is leading many clinicians to increasingly consider alternative agents. With respect to the thiazolidinediones, pioglitazone is now the only widely available agent, as rosiglitazone is only available in the United States with marketing restrictions. The thiozolidinediones are associated with well-recognized side effects including weight gain, fluid retention, precipitation of cardiac failure, and risk of bone fractures, especially in postmenopausal women.[65,68] The use of pioglitazone has also been related to bladder cancer in some studies, and this is currently being reviewed by the US FDA.[69] As a result, therefore, of the limitations of both sulfonylureas and thiazolidinediones, incretin-based therapies including GLP-1 and DPP-4 inhibitors offer significant potential advantages. In primary care, in particular, DPP-4 inhibitors are preferred over GLP-1 receptor agonists by many health care professionals, as they are a simple to administer oral agent as opposed to a subcutaneous injection. The FDC of metformin with a DPP-4 inhibitor is an attractive treatment option for metformin failure patients or where a high HbA_{1c} is present at presentation. As previously mentioned, there is concern about pancreatitis with use of incretin-based therapies, although a causative role has not been established. While the FDC of metformin and sitagliptin seems a logical treatment option, it would be advisable to exercise caution when prescribing it in patients at risk of pancreatitis, in keeping with the use of both DPP-4 inhibitors and GLP-1 receptor agonists.[34,39] The long-term cardiovascular safety studies of DPP-4 inhibitors, currently ongoing and also collecting data on pancreatitis rates, will hopefully help address some of these concerns.

Finally, as previously discussed, the higher acquisition cost of all new drugs is a critical issue in increasingly resource-limited health-care provision. The DPP-4 inhibitors are cheaper than GLP-1 receptor agonists but more expensive than other oral therapies. The acquisition cost of the FDC will also be a major determining factor when it comes to its place in our treatment algorithm.

Conclusion

From the currently available evidence, FDCs of metformin and sitagliptin have a beneficial effect on HbA_{1c}, fasting, and postprandial glucose. The fixed dose combination is convenient, is well tolerated with few side effects, demonstrates a low incidence of hypoglycemia, and does not lead to weight gain. The higher acquisition cost may, however, be a hurdle to prescribing. The DPP-4 inhibitor long-term safety studies are eagerly awaited and will undoubtedly impact on fixed dose combination development and use in the future.

Author Contributions

Wrote the first draft of the manuscript: CB. Contributed to the writing of the manuscript: SG. Agree with manuscript results and conclusions: SG. Jointly developed the structure and arguments for the paper: CB, SG. Made critical revisions and approved final version: SG. All authors reviewed and approved of the final manuscript.

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As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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