

## Combination Treatment of Oral Agents and Insulin in Type 2 Diabetes: A Narrative Review

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### Abstract

Type 2 diabetes (T2DM) necessitates early and effective treatment to delay or prevent micro- and macrovascular complications associated with diabetes. Monotherapy often fails after a period of treatment, so that multiple drugs are needed to achieve effective glycemic control. It is known that insulin is very effective in reducing hyperglycemia and may improve  $\beta$ -cell function in patients with T2DM. Based on the improved understanding of the pathophysiology and natural history of T2DM, insulin therapy should be introduced sooner rather than later to sustain glycemic targets. Adding oral antidiabetic drugs (OAD) to insulin can improve glycemic control and potentially lower the required insulin dose, resulting in less weight gain and lower risk for hypoglycemia. The treat-to-target algorithms of the recent studies combining OADs plus insulin have demonstrated that patients can reach glycemic treatment targets with low risk of hypoglycemia, greater convenience and with limited weight gain. This article presents the pharmacologic and physiologic aspects of combination treatment of oral agents with insulin in T2DM and elaborates current options available for this combination therapy. The evidence along with potential advantages and drawbacks of such regimens are discussed.

**Keywords:** Type 2 diabetes, Insulin, Oral antidiabetic agents, Combinations, Hypoglycemia

### Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and progressive  $\beta$ -cell dysfunction [1]. Consequently, most patients will need incrementally more complicated therapeutic regimens to control hyperglycemia, progressing through monotherapy, dual therapy, and commonly multi-agent therapy followed by insulin with or without other antidiabetic drugs [2]. Insulin is very effective in reducing hyperglycemia and can improve  $\beta$ -cell function in patients with T2 DM [3,4]. Physicians usually use insulin when glycemic control fails or is not maintained with combinations of antidiabetic medications. However, results from studies have shown the effectiveness of earlier use of insulin as add-on to an oral agent in patients with T2 DM [5,6]. This has stimulated discussions regarding the choice of agents which are best combined with insulin therapy [7].

The combination of insulin and oral agents has a definitive convenience and therapeutic benefits for patients. The benefits of combining basal insulin with oral agents for improved glycemic control are well established [8]. Conversely, adding oral agents

to insulin can potentially reduce the insulin dose required to meet therapeutic goals, resulting in less weight gain and lower risk for hypoglycemia. A number of different oral antidiabetic drugs (OADs) with different mechanisms of action are currently available. The differing attributes of oral agents in combination with insulin likely to provide an opportunity for the physician to better individualize care for patients with T2DM. Practical information and guidance is needed for clinicians to make clinical decisions about use of these agents in combination with insulin.

### Historical perspective

Combination treatment of insulin with sulphonylureas (SUs) was first used in the 1950s shortly after the introduction of tolbutamide [9]. Initially it was reported to have great success but it became apparent that its efficacy declines with time and by the 1960s combination treatment had fallen out of common use. With the introduction of new SUs in the 1970s, interest in insulin SU combination treatment was re-kindled. A number of studies which explored the effect of adding SUs to insulin-treated patients were published in the 1980s and early 1990s [10,11]. A meta-analysis of these studies concluded that combination treatment of insulin and SU results in a modest improvement in metabolic control (overall reduction in HbA1c was 1.1% in the SU-insulin group versus 0.3% in the placebo-insulin group), a modest insulin-sparing effect and possibly less weight gain [12].

Metformin, when given as adjunctive therapy, was well tolerated and improved glycemic control in patients on pre-existing insulin therapy whose diabetes was poorly controlled [13]. The FINFAT study [14] compared bedtime NPH insulin with various combinations of OADs. Self-adjustment of insulin dose and the addition of metformin produce slightly better overall glucose control than combination of bedtime insulin with glibenclamide or morning insulin or triple combination of bedtime insulin, metformin and glibenclamide.

### Rationale for Combination Therapy

Monotherapy or combination oral therapies are often unable to adequately achieve or maintain glycemic control in many patients with T2DM. As the number and dosage of oral agents increase, the side-effect profile, regimen complexity, and expense rise commensurately. The expected reduction in HbA1c with maximum doses of OADs in combination therapy is approximately 3.0% [15]. Accordingly, oral agents alone are unlikely to achieve treatment goals in patients presenting with HbA1c >10%. Combining insulin therapy with oral agents may allow patients to reach and maintain glycemic goals because ultimately oral agents alone cannot maintain glycemic control in many individuals [16].

### Pharmacologic and physiologic aspects

Achieving a better ratio of desired to undesired effects is the main benefit of combining anti-hyperglycemic agents together. While side effects are more common and prominent at maximal recommended dosage of most agents, most of the beneficial effects are evident at a much lower dosage. Combining two or more agents with different mechanisms of action at sub maximal dosage can achieve greater therapeutic power while reducing side effects. These principles are relevant to insulin as well [7]. Although glucose lowering power of insulin is unlimited, relentless increase in insulin dose increases the chance of hypoglycaemia. This can be reduced with timely use of combined therapy with oral agents.

Oral agents act by either increasing secretion or potentiating action of endogenous insulin, thus enhancing glycemic buffering. Insulin sensitizers (metformin and thiazolidinediones) are the agent of choice for this purpose as they help to reduce glycemic variability. They also potentiate the action of exogenous insulin and thus contribute to the reduction of dose needed. Another benefit of combining an insulin sensitizer with insulin is the lesser risk of hypoglycaemia while maintaining equal glycemic control as compared with insulin alone [7].

### Combination Therapy: Oral Agents as Add-on Therapies

Insulin in combination with OHAs can be used at either of two stages: [1] an OHA may be added to the treatment of a patient who is already on insulin; [2] alternatively, insulin therapy may be added to the treatment of patients who are failing to achieve target glycemic control with OHAs alone.

In the case of insulin combinations, addition of another agent should reduce the required dose of insulin and may result in less weight gain and hypoglycemia. Another advantage for combination

therapy relates to proven or potential benefits other than those resulting from better glycemic control (reduction in blood pressure, improving lipid profiles etc). This concept has been most emphasized for metformin and thiazolidinediones. Both of these classes of agents have potential non-glycemic effects that may reduce cardiovascular risk. When choosing an additional agent to be combined with insulin, it is argued that agents associated with hypoglycemia and/or weight gain should be avoided so as not to exacerbate these risks already present with insulin [2].

### Metformin

Metformin has clinical benefits beyond glycemic control, which are particularly pertinent to individuals with T2DM. In particular, insulin-related weight gain is minimized or even countered by combination with metformin [17]. The addition of metformin to pre-existing insulin therapy was first shown to have efficacy beyond that of continuing insulin alone in a study by Giugliano et al. [13]. Subsequently several studies have addressed this strategy with decrease in HbA1c between 1-2.5%. The largest HbA1c reduction was obtained with maximized intensive insulin therapy in patients with T2DM who were randomized to added metformin or placebo [18]. The goal of this study was to maximally decrease HbA1c with intensive insulin adjustments. HbA1c levels decreased by 2.5% in the metformin group, a significantly higher change than the decrease of 1.6% in the placebo group. When combined with insulin, metformin produces better glycemic control, less weight gain, lower insulin requirement (insulin-sparing effects ranging from 17 to 35%), and, in most cases, less hypoglycemia than insulin alone [19-21]. The benefits of metformin transfer to combination therapy. A metformin-biphasic insulin aspart 70/30 combination showed positive trends towards a reduction of cardiovascular risk factors compared with BIAsp 70/30 monotherapy in an open-label study in patients with T2DM [22]. Metformin appears to be an appropriate, well-tolerated, and effective adjunct to insulin therapy when used in the management of T2DM.

### Thiazolidinediones

Thiazolidinediones (TZDs) are effective in reducing HbA1c levels without inducing hypoglycemia and improve lipid profiles [23]. Thiazolidinediones have other clinically important non-glycemic benefits as well. Combination of a TZD and insulin enhances glycemic control and decreases insulin requirements versus insulin alone. However, compared with insulin alone, the combination increased weight and symptoms of hypoglycemia and edema [24-27]. Therefore, safety issues associated with an insulin-TZD combination include exacerbation of hypoglycemia and weight gain. However, such increases in bodyweight appear to primarily involve peripheral subcutaneous rather than visceral sites. There are relatively few published studies on the use of the triple combination therapy insulin+metformin+thiazolidinedione, which shows improved glycemic control as compared with insulin plus metformin or insulin plus TZDs groups [28]. The efficacy of triple combination therapy probably lies in its action on all three of the major pathophysiological defects of T2DM (peripheral insulin resistance, hepatic insulin resistance, and diminished insulin secretion following meals).

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## Sulfonylureas and Meglitinides

Although associated with weight gain, as monotherapy, these classes of compounds lead to excellent reduction in HbA1c. SUs have been shown to reduce microvascular complications but are associated with an increased risk of hypoglycemia [29,30]. To achieve similar glycemic control, the group with combined insulin and SU needed less insulin as compared with the group with insulin alone [31-33]. However, the SU plus insulin group experienced more hypoglycemic events and similar or greater weight gain than in the insulin-plus placebo groups. Furthermore, there is increased risk of all-cause mortality and cardiovascular death with insulin-SU combination compared with insulin metformin combination [34]. So this combination is becoming less favored by clinicians. It is suggested that SUs and meglitinides should be avoided when prandial or premixed insulin is used.

## Alpha glucoside inhibitors

Other approved agents that are infrequently used in the United States and Europe include  $\alpha$ -glucosidase inhibitors. Acarbose was shown to be an effective adjunct therapy in combination with insulin. After 24 weeks of treatment, HbA1c was reduced by 0.4%, and insulin requirements were substantially lowered in patients in whom acarbose was added to their insulin regimen vs those remaining on insulin monotherapy [35]. A similar trial demonstrated a 0.69% HbA1c reduction as well as significant reductions in postprandial glucose and triglyceride levels with the addition of acarbose to existing insulin therapy [36]. The body weight benefits of acarbose treatment may also be beneficial when this drug is prescribed alongside insulin [37].

## Newer drugs

Dipeptidyl peptidase-4 inhibitors (DPP-4) and Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are newer classes of agents.

Approved dipeptidyl peptidase-4 inhibitors (DPP-4) inhibitors include sitagliptin, saxagliptin, linagliptin, vildagliptin (European Union only), and alogliptin. As a group, DPP-4 inhibitors decrease HbA1c levels, FPG, and PPG. They have also been shown to improve a surrogate of  $\beta$ -cell function as determined by homeostatic model assessment- $\beta$  (HOMA- $\beta$ ) [38-40]. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are an emerging class of oral antidiabetic medications that reduce hyperglycemia in an insulin-independent manner. Canagliflozin and empagliflozin in the United States and Dapagliflozin in Europe have recently gained approval for the treatment of T2DM.

## DPP-4 inhibitors as add-on therapy to insulin

Sitagliptin, saxagliptin, vildagliptin, alogliptin, or linagliptin added to insulin therapy (with or without metformin) produced greater reductions in HbA1c (placebo-corrected values, -0.60, -0.41, -0.30, -0.58, and -0.65%, respectively) and PPG than insulin alone [41-45]. At study end, the increment in daily insulin requirement in patients group receiving a DPP-4 inhibitor was numerically lower as compared with placebo group. Changes in body weight were similar between placebo and DPP-4 inhibitor groups. The incidence of hypoglycemia in patients receiving a DPP-4 inhibitor

plus insulin versus insulin alone, however, varied across the studies [41-43]. DPP-4 inhibitor as an add-on to insulin therapy is expected to improve glycemic control without any apparent increase in hypoglycemia risk and weight gain.

## SGLT-2 inhibitors as add-on therapy

Wilding, et al. reported that dapagliflozin (10 mg/day) when added to insulin therapy, reduced HbA1c by -0.96%, compared with a change of -0.39% with placebo [46]. Body weight was reduced by 1.6 kg with dapagliflozin versus an increase of 0.4 kg with placebo. Reduction in daily insulin dose was higher in patients treated with dapagliflozin 10 mg/day, compared with those receiving placebo (difference [95% CI] from placebo -6.82 IU [-9.56, -4.09]). The effects of dapagliflozin on glycemic parameters, body weight, and insulin use were maintained for at least 48 weeks. The percentage of patients with  $\geq 1$  episode of hypoglycemia was slightly higher in those receiving dapagliflozin.

The ongoing, randomized, placebo-controlled Canagliflozin Cardiovascular Assessment Study (CANVAS) is investigating the difference in the risk for cardiovascular disease between patients treated with canagliflozin and those given placebo. A recent finding from this study indicated that the addition of canagliflozin to insulin therapy improved glycemic control and reduced body weight [47]. The latest SGLT 2 inhibitor, Empagliflozin also demonstrated improved glycemic control and reduced weight with a similar risk of hypoglycemia to placebo when added to basal insulin for 78 weeks [48]. Addition of SGLT 2 inhibitors to insulin can counter the weight gain and fluid retention associated with high insulin dose. Significant weight loss was also observed when SGLT 2 inhibitors were added to insulin. However, caution should be taken while combining SGLT 2 inhibitors with insulin in more advanced T2 DM with significant beta cell failure since there is potential risk of euglycemic diabetic ketoacidosis (DKA) if insulin dose is lowered too much [49].

## Combination of Oral Agents Plus Once-daily Insulin

Our improved understanding of the natural history of T2DM suggests that insulin therapy should be started sooner rather than later and that insulin should be viewed as an essential therapeutic tool for achieving disease management goals, at an earlier stage in the natural progression of the disease. Patients who are not at target HbA1c or no longer respond adequately to oral agents will benefit from combination therapy that consists of maintaining the use of oral anti-diabetic agents together with supplemental insulin therapy.

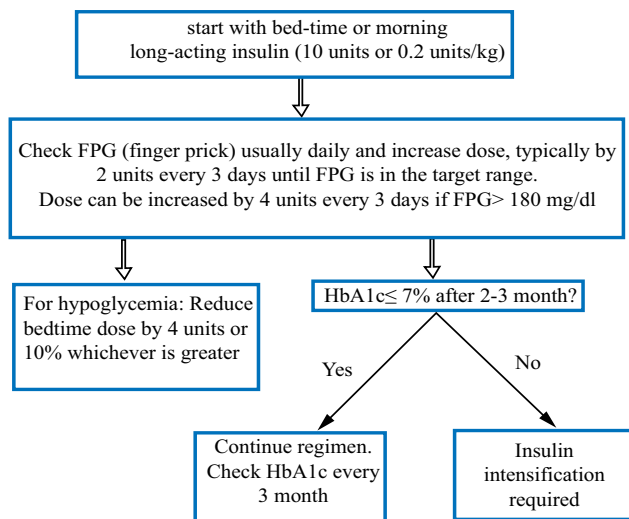
There is an abundance of clinical evidence that supports combining insulin with oral agents to improve glycemic control. The initiation of basal insulin has demonstrated efficacy for improving glycemic parameters in combination with oral agents. Basal insulin replacement improves not only fasting plasma glucose (FPG) but also results in improved postprandial glucose (PPG). Since PPG excursions are, effectively, superimposed peaks on basal (interprandial) glucose levels, the efficacy of insulin glargine in lowering basal glucose levels favorably impacts postprandial levels

throughout the day [50].

FINFAT study involving patients with poor glycemic control on SU showed that metformin plus once-daily insulin was significantly more effective than insulin plus glibenclamide, insulin plus glibenclamide and metformin, or additional insulin (a second injection) [14]. The insulin plus metformin group also had less symptomatic and biochemical cases of hypoglycemia and did not experience weight gain. In the Veterans Affairs Cooperative Study-Diabetes Mellitus, results demonstrated that a single injection of evening NPH insulin in combination with glipizide, as part of an intensive insulin therapy regimen in patients poorly controlled on other pharmacologic therapies, maintained near normal glycemic control [51]. Large interventional trials with different insulin regimens demonstrated non-inferiority of basal insulin analogs (either glargine or detemir) in achieving an HbA1c target  $\leq 7\%$  compared with prandial or premixed insulin when added to OADs [52,53]. However, the basal insulin regimens were associated with significantly fewer hypoglycemic events, less weight gain and improved patient treatment satisfaction compared with either prandial or premixed insulin regimens [52,53].

### Adding a basal insulin to OADs

The usual way to start insulin therapy is with a basal insulin, although some patients may start with a premixed insulin. For this purpose, the American Diabetes Association's treatment algorithm for the initiation and adjustment of insulin regimens can be used as a very useful guide (Figure 1).



**Figure 1:** Initiation of basal insulin regimens and self-titration algorithm.

They suggest a treat to target regimen; to start low dose basal insulin and titrated upwards until glycemic control is achieved, targeting FPG levels [2]. Once-daily dosing of basal insulin with continued use of one or more OHAs is an effective and safe glucoselowering treatment in most insulin-naïve patients. The advantages of adding once daily basal insulin to prior treatment with oral agents include the following: Only one insulin injection may be required each day,

with no need for mixing different types of insulin; Titration can be accomplished in a slow, safe and simple fashion; Combination therapy eventually requires a lower total dose of insulin. The use of insulin pens can enhance patient acceptance [1-4]. The result is effective improvement in glycemic control while causing only limited weight gain. Adding insulin in the evening is a simple and effective strategy that can be regarded as “bridge therapy”. It allows patients to overcome their initial resistance to start using insulin, facilitating long-term acceptance and compliance.

To summarise, the comparison of different OHA combinations with insulin in T2DM is shown in Table 1 [54].

|   | HbA1c changes (%) | Weight changes (lb) per 1% A1c reduction |
|---|-------------------|--|
| <b>Widely used values from systemic meta-analysis</b>     |                   |  |
| Basal insulin added to:                                   |                   |  |
| Metformin   | -2.5              | +1                                       |
| Sulfonylurea  | -2.1              | +5                                       |
| Metformin + Sulfonylurea                                  | -1.9              | +3                                       |
| <b>Less often used values from systemic meta-analysis</b> |                   |  |
| Metformin added to insulin                                | -1.9              | -1                                       |
| Sulfonylurea added to insulin                             | -1.4              | +3                                       |
| Glitazones added to insulin                               | -1.3              | +8                                       |
| <b>Less often used values from limited studies</b>        |                   |  |
| $\alpha$ -glucosidase inhibitors added to insulin         | -0.6              | 0  |
| Gliptin added to insulin                                  | -0.3              | +1                                       |

**Table 1:** The different OHA combinations with insulin and their effects.

### Continuation versus discontinuation of insulin secretagogues when initiating insulin

Combining a SU with bedtime long or intermediate acting insulin is an effective strategy to improve glucose control and to overcome secondary SU failure. The rationale of combination therapy with SU and insulin is based on the assumption that, if bed time insulin (BI) lowers the fasting glucose concentration to normal, then daytime SUs (DS) will have a more effective control of postprandial hyperglycemia throughout the day [55]. However, the utility of combining insulin with a sulfonylurea remains controversial [56]. Moreover, the discussion is hampered by a lack of well-controlled clinical trials examining this issue in the context of treatment with modern insulin preparations and systematic titration algorithms. An established body of evidence gathered over the past 30 years indicates that the clinical benefits (metabolic improvement and glycemic control) of combining insulin with a SU are transient and, at best, marginal, failing to produce near-normal glucose concentrations [57,58].

A recent study addressing this issue concluded that in patients with T2DM starting basal insulin analogue therapy, continuing both metformin and insulin secretagogues resulted in more hypoglycemia and weight gain and only lowered daily insulin

doses than maintaining only metformin in combination with basal insulin [59]. Current evidence suggests that such combinations are of limited clinical value in patients with T2DM poorly controlled by either insulin or oral anti-diabetic drug monotherapy. In absence of controlled trials, it is still debated whether insulin secretagogues should be retained when initiating insulin in T2DM.

### Practical Suggestions for Combination Therapy

Basal insulin should be the initial choice along with existing oral therapy when oral therapy alone or in combination fails to attain or maintain glycemic goals. Cessation of oral therapy while titrating basal insulin is less desirable, as the basal insulin is not empowered with modulating postprandial glucose excursions. When initiating basal insulin, 10 units or 0.2 unit/kg body weight of either NPH insulin, insulin glargine, or insulin detemir is an appropriate beginning dose. There are many factors the physician should take into account when making clinical decisions regarding choice of basal insulin for combination therapy including convenience, control of postprandial glucose levels, hypoglycemia incidence, avoiding weight gain, and achieving a more physiologic insulin profile. Convenience may be incorporated into insulin regimens by use of once-daily options. Factors such as side-effect profile, cardiovascular safety, cost, and patient's preference should be considered and balanced with the expected benefits of adding oral drugs. Table 2 provides a summary of factors that may affect choice of oral agents and suggested choices for oral therapies. Finally, the contribution of FPG and PPG to overall hyperglycemia should be considered. Thus a patient with a relatively low HbA1c may benefit more with an agent that targets PPG.

| Clinical factors                                    | Oral agent for combined therapy with insulin  |
|---|---|
| Efficacy  | Sulfonylureas, metformin, and thiazolidinediones  |
| Minimizing cost                                     | Least expensive: sulfonylureas; most expensive: DPP-4 inhibitors, SGLT-2 inhibitors   |
| Weight gain   | Metformin, alpha-glucosidase inhibitors, SGLT-2 inhibitors  |
| Least risk of hypoglycemia                          | Metformin, thiazolidinediones, DPP-4 inhibitors, alpha-glucosidase inhibitors   |
| Improvement of insulin resistance                   | Metformin and thiazolidinediones  |
| Patient and provider effort                         | Once-daily metformin or sulfonylureas   |
| Hepatic impairment                                  | Metformin, sulfonylureas, DPP-4 inhibitors, alpha-glucosidase inhibitors  |
| Abnormal renal function or congestive heart failure | Sulfonylurea or other secretagogues (caution should be exercised in patients with renal impairment)                                     |
| Convenience   | Sulfonylureas, thiazolidinediones, metformin, or combination of metformin and glimepiride; or combination of metformin and pioglitazone |

**Table 2:** Candidates for oral antidiabetic agents in combined therapy with insulin.

### Summary and Conclusion

The progressive nature of T2DM almost always necessitates treatment intensification as  $\beta$ -cell function decreases. Continuation of antidiabetic medications after initiating insulin therapy or the addition of other antidiabetic medications to existing insulin therapy improves glycemic control. Several studies have proven superior glycemic control with combined therapy with insulin plus oral agents and it is now being widely used in clinical practice. Nevertheless, combined therapy with oral agents and insulin has not been accepted as desirable by all experts. The rationale for using combined regimens to minimize the dosage of antihyperglycemic agents and thereby their unwanted effect is clear. Ideally, combination therapy should be individualized to match patient baseline HbA1c, lifestyle, comorbidities, economics, insulin requirements, personal preference, and patient convenience. Treatment with insulin provides replacement therapy that complements the insulin-sensitizing action of metformin and thiazolidinediones. Secretagogues can work with exogenous insulin by raising endogenous insulin levels. However, it is still debated whether insulin secretagogues should be retained when initiating insulin. Newer classes of oral antidiabetic medications such as DPP-4 inhibitors, and SGLT2 inhibitors, improve glycemic control when combined with insulin therapy. They have added benefits over older drug classes because they are weight reducing or and have a low propensity to cause hypoglycemia. The multiplicity of oral drugs available for use with insulin need not be viewed as confounding, but rather as an opportunity to individualize and intensify care for patients with T2DM.

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