



Insulin Monotherapy Versus Insulin Combined with Other Glucose-Lowering Agents in Type 2 Diabetes: A Narrative Review

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Abstract

Context: Insulin can be prescribed as a monotherapy or a combined therapy with other anti-diabetic medications. In this narrative review, the authors aimed to gather data related to comparison of insulin monotherapy versus combination of insulin and other anti-diabetic treatments with regards to different outcome measures in type 2 diabetes.

Evidence Acquisition: This study searched and focused on the most recently published systematic reviews and their references investigating issues related to the primary aim.

Results: The current data available on this topic is heterogeneous and suffers from low quality with respect to most combination treatments. Considering the efficacy and safety of combination therapy of insulin with older hypoglycemic agents, in general metformin and pioglitazone have the best and worst profiles, respectively. Compared to insulin monotherapy, combination of insulin and metformin is associated with better glycemic control, reduced daily insulin dose, less hypoglycemia, and weight gain; combination of insulin and pioglitazone results in greater hypoglycemia and weight gain and is associated with increased risk of edema and heart failure. Regarding sulphonylurea, there is some concern regarding hypoglycemia and weight gain. Addition of dipeptidyl peptidase-4 inhibitors to insulin seems to be beneficial with respect to glycemic control without any significant adverse effects. New drugs, including glucagon-like peptide-1 agonists and sodium glucose co-transporter 2 inhibitors, have acceptable profiles with significant benefits regarding weight reduction when added on insulin therapy.

Conclusions: Considering the quality and longevity of evidence, compared to insulin monotherapy, insulin combined with metformin and pioglitazone has the best and worst profiles, respectively. New anti-diabetic medications have acceptable profiles yet are expensive. It is important for clinicians to meticulously weigh the advantages of combination therapy against the possible adverse effects with each drug class in every patient, individually.

Keywords: Insulin, Metformin, Sulphonylurea, Pioglitazone, DPP-4 Inhibitor, GLP-1 Agonist, SGLT2 Inhibitor, Type 2 Diabetes Mellitus

1. Context

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by worsening pathophysiology. With currently available anti-diabetic therapies, most of them not being disease modifying, pancreatic β -cell mass and function decrease over time (1), and the usual course of therapeutic approach for patients with T2DM is sequential addition of hypoglycemic agents with different mechanisms of action followed by insulin therapy (2).

Insulin can be prescribed as a monotherapy or a combined therapy with other anti-diabetic medications. A desired diabetes treatment protocol includes use of medications that in parallel with optimal glycemic control, do not have significant adverse effects; two of these adverse

effects, hypoglycemia and weight gain, are amongst important barriers of insulin initiation or intensification (3). Moreover, consideration of patient-important outcomes resulting from vascular complications of DM has been emphasized to be incorporated in diabetes care protocols (4) and should be acknowledged in management strategies of patients with diabetes.

Until now, two Cochrane systematic reviews regarding comparison of insulin monotherapy versus insulin combined with oral hypoglycemic agents have been conducted on patients, who were insulin-naive (5) and those, who were already on insulin therapy (6). Based on their date of publication and protocol, these comprehensive and sophisticated systematic reviews did not include

new anti-diabetic therapies, including Sodium glucose co-transporter 2 (SGLT2) inhibitors and injectable hypoglycemic agents other than insulin, i.e. glucagon like peptide 1 (GLP-1) agonists.

In this narrative review, the authors aimed to gather data related to comparison of insulin monotherapy versus combinations of insulin and other anti-diabetes treatments with regards to different outcome measures, including a) glycemic control, b) required daily insulin dose, c) adverse events, d) diabetes-related morbidity, e) health-related quality of life and patient satisfaction, and f) mortality.

2. Evidence Acquisition

The terms (insulin) AND (hypoglycemic) OR (antidiabetic) OR “glucose-lowering” OR (sulphonylurea) OR (metformin) OR (pioglitazone) OR “DPP-4 inhibitor” OR “DPP4 inhibitor” OR “GLP-1 agonist” OR “GLP-1 receptor agonist” OR “SGLT2 inhibitor” were used to search review articles in Pubmed, Scopus, and Cochrane library up to 01 September 2017. The researchers focused on the most recently published systematic reviews and their references investigating issues related to the primary aim. With regards to the scarce data available on the comparison of insulin monotherapy versus combinations of insulin with new medication classes, addition of these drugs to any insulin-based therapies has been considered.

3. Results

3.1. Insulin Monotherapy Versus Insulin Plus Sulphonylurea

In the 2004 Cochrane systematic review (5), Goudswaard et al. included 20 randomized controlled trials (RCTs) (7-15) (16-25) with follow-up durations of 2 months to 3 years (mean 10 months). Primary outcomes were any diabetes-related morbidity and glycemic control. Secondary outcomes included quality of life, patient satisfaction, insulin requirement, and adverse effects. Methodological quality of studies was low. Not all, but most trials included studies comparing insulin monotherapy regimens with combinations of insulin and sulphonylurea with or without metformin. Only one study used an insulin analogue, lispro insulin (25). Regarding glycemic control, meta-analysis of 5 studies with low heterogeneity (16%) showed that bedtime neutral protamine Hagedorn (NPH) insulin plus sulphonylurea

was associated with lower HbA1c compared with once daily NPH insulin alone (mean difference: 0.33% [95% CI 0.03, 0.62]); when the comparison included twice-daily insulin monotherapy regimens, this difference abated. With respect to other outcomes, insulin-sulphonylurea (\pm metformin) combination therapy versus insulin monotherapy in insulin-naive patients resulted in 43% relative reduction in total daily insulin requirement; no significant difference in the frequency of symptomatic or biochemical hypoglycemia and weight gain was detected. Quality of life was assessed in 4 studies (16, 21-23) and no significant differences were reported between groups. None of the mentioned studies investigated diabetes-related morbidity or mortality.

Recently, the Cochrane group published a systematic review with the aim of assessing the effects of addition of oral hypoglycemic agents to insulin monotherapy (6). The main difference between this review protocol and older ones was the manner, according to which they included trials with patients already on insulin therapy. Primary outcomes included all-cause mortality, diabetes-related morbidity, and adverse events. With regards to different sulphonylureas, including glibenclamide, glipizide, tolazamide, gliclazide, and glimepiride, 17 trials (26-41) had low quality evidence, and compared combination therapy with insulin monotherapy; mortality and morbidity were not evaluated in any trials. Regarding patient satisfaction, results of the Switch pilot study showed no differences between insulin-glimepiride therapy and insulin monotherapy (31). The main findings of analyses related to other outcomes have been depicted in Table 1.

Taken together, findings of 2 Cochrane systematic reviews mentioned above indicate that the additional effect of the combination of insulin with sulphonylurea on glycemic control in insulin-naive patients seems to be small; regarding the effectiveness of sulphonylurea-insulin combination compared to insulin monotherapy, it is important to note whether patients are insulin-naive or already on insulin therapy.

3.2. Insulin Monotherapy Versus Insulin Plus Metformin

In 2012, Hemmingsen et al. reported results of a meta-analysis on 23 RCTs (24, 42-52) (53-67) with 2,117 participants, investigating the efficacy and safety of metformin and insulin versus insulin therapy alone (68). Primary outcomes were all cause mortality and cardiovascular mortality. Secondary outcomes were macrovascular and microvascular

Table 1. Pooled Effects of Addition of Sulphonylurea to Insulin Versus Insulin Monotherapy^a

Outcome	Insulin Monotherapy	Insulin-Sulphonylurea
Mean difference in HbA1c, %	-	-1 (95% CI: -1.6 to -0.5)
Mild hypoglycemic episodes per participant	2.0 to 2.6	2.2 to 6.1
Additional weight gain, kg	-	0.4 to 1.9

Abbreviations: CI: confidence interval; HbA1c, glycosylated hemoglobin.

^aData derived from reference 6.

diseases, adverse events, cancer, quality of life, costs, insulin dose, glycemic control, weight, and blood pressure. Based on bias risk assessment of this review, all trials had high risk of bias. Duration of studies was between 3 to 24 months. Regarding the random effects model, combined insulin-metformin therapy resulted in greater HbA1c reduction (mean difference: -0.6% [95% CI -0.89 to -0.31]) accompanied with reduced insulin dose (mean difference: -18.65 units/day [95% CI -22.7 to -14.61]) and less weight gain (mean difference: -1.68 kg [95% CI -2.22 to -1.13]), compared to insulin alone. There was no significant difference in the frequency of severe or mild hypoglycemia or other adverse events. Data regarding primary outcomes was sparse and combination therapy did not significantly affect all-cause mortality (5 trials (24, 58, 62, 63, 67), relative risk 1.30, 95% CI 0.57 to 2.99) or cardiovascular mortality (3 trials (58, 62, 63), relative risk 1.70, 0.35 to 8.30). Based on 3 trials, macrovascular complications were similar; only one trial reported data for composite microvascular outcome, which was not different (63). For quality of life, only 3 trials were found, all of which reported no significant difference between the 2 treatment groups (56, 59). Trial sequential analysis revealed sufficient evidence for HbA1c reduction of 0.5%, lower weight gain of 1 kg, and lower insulin dose of 5 units/day for combined insulin and metformin therapy versus insulin therapy alone. Findings of a recent Cochrane systematic review (6) regarding insulin-metformin therapy versus insulin monotherapy were in agreement with those of Hemmingsen et al.'s systematic review, except regarding Gastrointestinal (GI) adverse effects. Vos et al. reported higher GI complaints with combination therapy (7% to 67%) compared to insulin monotherapy (5% to 16%) (6).

3.3. Insulin Monotherapy Versus Insulin Plus Pioglitazone

According to Vos et al.'s systematic review (6), data for comparison of the efficacy and safety of combined insulin-

pioglitazone therapy with insulin monotherapy, from 3 trials (69-71), was rated as low-quality evidence. Regarding glycemic control, it was not possible to run a meta-analysis. Overall glycemic control was comparable in the 2 groups. Insulin plus pioglitazone therapy was associated with both increase in mild to moderate hypoglycemic episodes and weight gain (3.8 kg [95% CI 3.0 to 4.6]) and a small reduction in total daily insulin requirement compared to insulin alone; more cases of dose-dependent edema (69, 70) and heart failure (69) were also observed.

3.4. Insulin Monotherapy Versus Insulin Plus Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Based on a recent Cochrane review (6), low-quality evidence from 3 trials using vildagliptin (72), sitagliptin (73), and saxagliptin (74) documented slightly better glycemic control in the insulin-DPP4 inhibitor group (mean difference in HbA1c: -0.4% (-0.5 to -0.4)) associated with no significant difference in total daily insulin requirement and weight gain. Heterogeneous data regarding hypoglycemic episodes was in favor of lower rates of these episodes in the combination therapy group.

3.5. Insulin Plus SGLT2 Inhibitors

Efficacy and safety of adding SGLT2 inhibitors, as the most recently developed oral anti-diabetic agents, on insulin therapy have been investigated by several studies, none of which compared the combination therapy with a placebo group receiving insulin monotherapy. Summarizing data derived from these studies with durations ranging from 12 to 104 weeks considered in a recent review (75), yielded the following results: SGLT2 inhibitors when added on insulin could result in improved glycemic control (range of HbA1c difference: -0.4 to -1.1%) associated with reduced daily insulin requirement and weight reduction (1.2 to 4.5 kg). It should be noted that in some studies,

this combination resulted in elevated incidence of hypoglycemia.

3.6. Insulin Plus GLP-1 Agonists

Findings of a meta-analysis of 15 RCTs with 4,348 participants (76-90) assessing different outcomes of basal insulin-GLP-1 agonist combination therapy compared to other hypoglycemic agents (91) demonstrated that combined treatment results the followings: 1) greater reduction in HbA1c (0.44% [95% CI 0.29 - 0.6]); 2) greater proportion of participants achieving HbA1c \leq 7%; 3) no increased relative risk of hypoglycemia (0.99; 95% CI 0.76 to 1.29); and 4) higher weight reduction (mean difference: -3.22 kg [95% CI -4.90 to -1.54]). Compared to basal-bolus insulin regimens, the combination of GLP-1 agonist and basal insulin leads to slightly better glycemic control (mean difference in HbA1c: -0.1% [-0.17 to -0.02]), yet no benefit regarding proportion of participants achieving HbA1c \leq 7%; regarding this comparison, insulin plus GLP-1 agonists resulted in lower risk of hypoglycemia (RR 0.67, 95% CI 0.56 to 0.80) and greater weight reduction (-5.66 kg; 95% CI -9.8 to -1.51).

Recently, Maiorino et al. compared GLP-1 agonists alone or as titratable fixed-ratio plus basal insulin with other injectable treatments (92); 26 RCTs (76-84) (86-88, 93-106), lasting 12 to 52 weeks and involving 11,425 patients were included in this meta-analysis, yet the results had high heterogeneity and a significant publication bias. Insulin plus GLP-1 agonists versus other injectable therapies resulted in greater reduction of HbA1c (mean difference: -0.47%, 95% CI -0.59 to -0.35), more patients at HbA1c target (RR: 1.65, 95% CI 1.44 - 1.88), similar hypoglycemic events (RR: 1.14, 95% CI 0.93 - 1.39), and greater weight reduction (mean difference: -2.5 kg, 95% CI -3.3 to -1.7). Compared with basal-bolus insulin regimens, insulin plus GLP-1 agonists produced comparable glycemic control, less hypoglycemia (RR: 0.66, 95% CI 0.46 to 0.93), and greater weight reduction (mean difference: -4.7 kg, 95% CI -6.9 to -2.4).

4. Conclusions

Current data available on this topic is heterogeneous and suffers from low quality with respect to most combination treatments. Based on the findings presented in Table 2, considering the efficacy and safety of combination therapy of insulin with older hypoglycemic agents, generally, metformin and pioglitazone have the best and worst profiles, respectively. Compared with insulin monotherapy,

combination of insulin and metformin is associated with better glycemic control, reduced daily insulin dose, less hypoglycemia, and weight gain; combination of insulin and pioglitazone results in greater hypoglycemia and weight gain and has increased risk of edema and heart failure. Regarding sulphonylurea, there is some concern about hypoglycemia and weight gain. Addition of dipeptidyl peptidase inhibitors to insulin seems to be beneficial with respect to glycemic control without any significant adverse effects. New drugs, including glucagon like peptide-1 agonists and sodium glucose co-transporter 2 inhibitors, have acceptable profiles with significant benefits regarding weight reduction when added on insulin therapy.

It should be noted that this research did not undertake a systematic search on this subject. Although qualified systematic reviews included in the review covered most related evidence, there is certainly concern regarding missing available evidence related to the topic.

In conclusion, when considering a patient receiving insulin or scheduled for initiation of insulin therapy, decision-making about concomitant use of other hypoglycemic medications needs attention and must be based on different patient characteristics and his/her disease status. It is important for clinicians to meticulously weigh the advantages of combination therapy against possible negative effects in every patient on an individual basis. Data available on the efficacy and safety of insulin plus other anti-diabetic agents have low quality and some outcomes, including microvascular complications of DM, cardiovascular morbidity and mortality, and patient-reported outcomes, have not been assessed and should be considered in future research studies.

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Footnotes

Conflicts of Interest: The authors declare no conflicts of interest.

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Table 2. Effects of Addition of Different Glucose Lowering Agents to Insulin Regimens

Anti-Diabetic Agent	Outcome Measures					Monthly Cost	
	Glycemic Control	Required Daily Insulin	Hypoglycemia	Weight Gain	Other Adverse Effects	US, \$ ^{a,b}	Iran, Tomans ^a
Sulphonylurea	+ or ND	+	- or ND	- or ND	None	93	6,000
Metformin	+	+	+	+	Gastrointestinal	84	10,800
Pioglitazone	ND	+	-	-	Edema, Heart failure	348	14,400
DPP-4 inhibitors	+	ND	+ or ND	ND	None	477	60,000
SGLT2 inhibitors	+	+	- or ND	+	None	517	Not available
GLP-1 agonists	+ or ND	+	+	+	None	968	840,000

Abbreviations: DPP-4, Dipeptidyl peptidase-4; GLP-1, Glucagon like peptide-1; ND, no difference; SGLT2, sodium glucose co-transporter 2; +, in favor of benefit of combination therapy; -, in favor of monotherapy.

^aEstimated cost of maximum approved daily dose.

^bData derived from American diabetes association standards of medical care in diabetes-2018.

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