Efficacy and safety of dipeptidyl peptidase-4 inhibitors: systematic review and meta-analysis.

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Background

- Clinical practice guidelines recommend metformin as first-line pharmacological therapy in type 2 diabetes mellitus (T2DM) patients and the addition of another antidiabetic agent [sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP-4), inhibitor glucagon-like peptide-1 (GLP-1) agonist or basal insulin] if glycemic control is not achieved. The agents choice depends on different aspects including the reduction of HbA1c, risk of hypoglycemia, weight changes, adverse effects or cost in a patient-centered aproach[1].

- Vildagliptin, sitagliptin, saxagliptin and linagliptin are DPP-4 inhibitors approved for use in T2DM patients in recent years. It is important to assess their effects for lowering HbA1c and fasting plasma glucose (FPG) levels, hypoglycemia risk or weight changes compared with other available antidiabetic agents.

Objective

- To determine the efficacy and safety of DPP-4 inhibitors in T2DM patients according to published data.

Materials and methods

- A systematic review of randomized clinical trials (RCT) in MEDLINE, Cochrane, ISI WOK, SCOPUS and clinicaltrials.gov databases was performed.

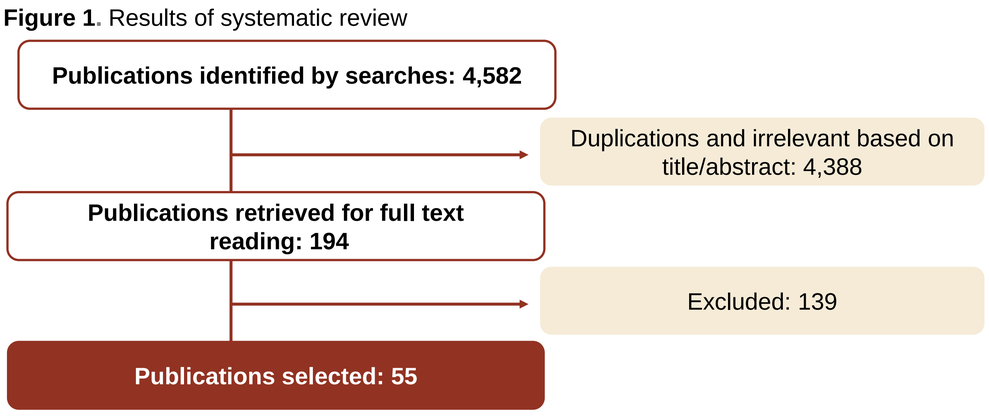
- Eligible studies were RCT with a treatment duration of at least 24 weeks evaluating efficacy (HbA1c, FPG and weight changes from baseline) and/or safety (hypoglycemia rate) of DPP4 inhibitors (vildagliptin, linagliptin, saxagliptin, sitagliptin) compared to placebo or non-insulin monotherapy or combination. These studies were published in English or Spanish until June 2013.

- Several meta-analysis were conducted using random effects models. Standardized mean difference (SMD) for efficacy variables and relative risk (RR) for safety variable with 95% confidence intervals (CI) were calculated[2]. Heterogeneity between studies was assessed by I^2 statistic. I^2 values of 25%, 50% and 75% were interpreted as low, moderate and high heterogeneity, respectively[3].

Results

- Of the 4,582 publications identified, 55 RCT were selected (Figure 1).

Figure 1. Results of systematic review



- The main characteristics of studies showed that most of them were published between 2006 and 2009; the number of study participants varied mostly between 501 and 1,000, and a total 5 points in the Jadad scale was assigned to most publications (Table 1).

Table 1. Main characteristics of studies selected

Characteristics of studies	% of studies
Year of publication	49% 2010 -2013; 51% 2006 -2009
Number of participants	24% <500 participants; 49% 501-1,000 participants; 27% >1,000 participants
Jadad scale	82% 5 points; 16% 4 points; 2% 1 point

- Comparisons extracted from clinical trials were classified in DPP-4 inhibitors vs. placebo (n=8); DPP-4 inhibitors vs. metformin (n=6); DPP-4 inhibitors+metformin vs. metformin (n=15); DPP-4 inhibitors+sulfonylurea vs. metformin+sulfonylurea (n=9); and DPP-4 inhibitors+sulfonylurea vs. sulfonylurea (n=3).

DPP-4 inhibitors vs. placebo

- DPP-4 inhibitor monotherapy was associated to greater reductions in HbA1c and FPG compared with placebo (Table 2).

Table 2. Meta-analysis results of DPP-4 vs. placebo

Efficacy and safety measures	SMD (95% CI)	RR (95% CI)	I^2
HbA1c change	-0.60 (-0.75; -0.46)	--	72.2%
FPG change	-0.51 (-0.62; -0.39)	--	0.0%
Weight change	0.11 (-0.06; 0.29)	--	59.6%
Hypoglycemia incidence	--	0.88 (0.32; 2.45)	0.0%

DPP-4 inhibitors vs. metformin

- DPP-4 in monotherapy compared with metformin showed lower reductions in HbA1c, FPG and weight (Table 3).

Table 3. Meta-analysis results of DPP-4 vs. metformin

Efficacy and safety measures	SMD (95% CI)	RR (95% CI)	I^2
HbA1c change	0.28 (0.20; 0.36)	--	8.4%
FPG change	0.36 (0.27; 0.44)	--	23.3%
Weight change	0.42 (0.33; 0.50)	--	24.1%
Hypoglycemia incidence	--	0.68 (0.37; 1.22)	0.0%

DPP-4 inhibitors + metformin vs. metformin

- DPP-4 inhibitors added to metformin lowered HbA1c and FPG levels significantly more than metformin monotherapy (Figure 2 and 3).

Figure 2. Forest plot for meta-analysis of HbA1c change of DPP-4+metformin vs. metformin

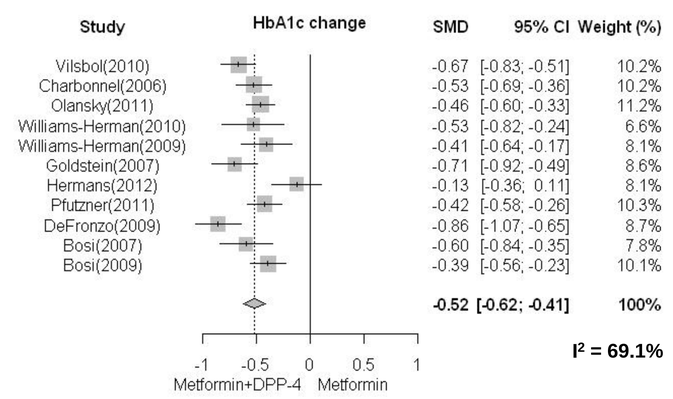
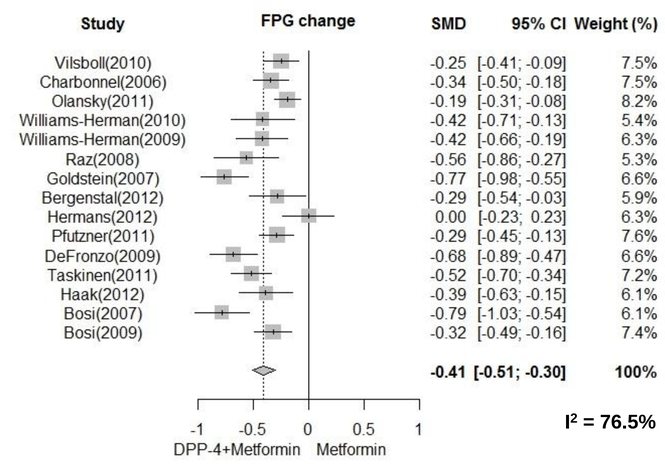


Figure 3. Forest plot for meta-analysis of FPG change of DPP-4+metformin vs. metformin



- Results on weight changes and hypoglycemia rate were not significantly different (weight SMD=0.03; 95% CI: 0.46; 1.32; hypoglycemia RR=0.78; 95% CI: 0.46; 1.32).

DPP-4 inhibitors + metformin vs. sulfonylurea + metformin

- DPP-4 added to metformin achieved a greater decrease in weight and hypoglycemia risk compared to sulfonylurea plus metformin (Figure 4 and 5).

Figure 4. Forest plot for meta-analysis of weight change of DPP-4+metformin vs. sulfonylurea+metformin

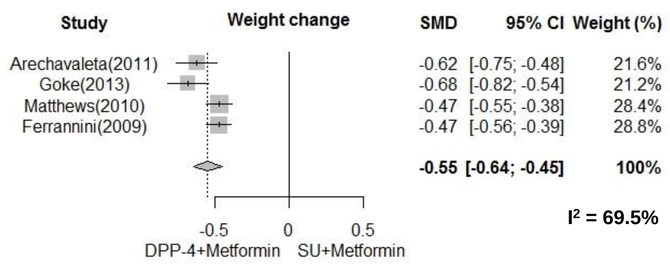
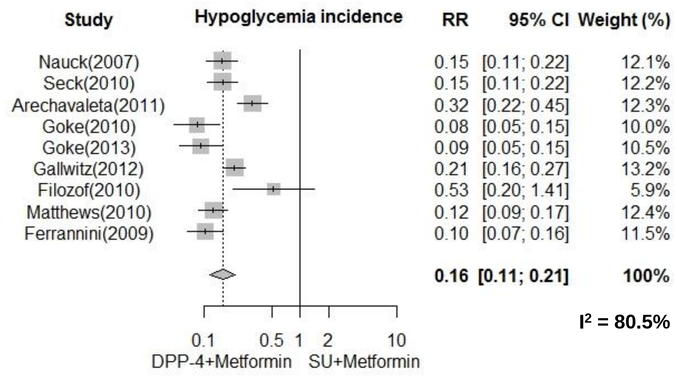


Figure 5. Forest plot for meta-analysis of hypoglycemia incidence of DPP-4+metformin vs. sulfonylurea+metformin

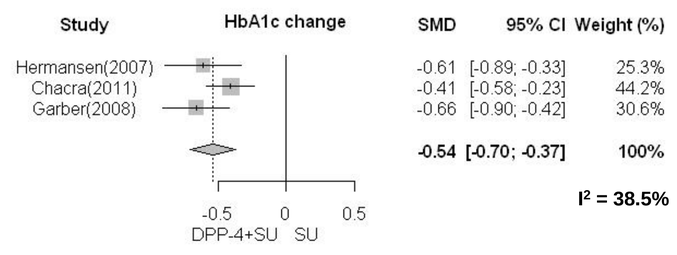


- Results on HbA1c and FPG changes were not significantly different (HbA1c: SMD=0.07; 95% CI: -0.01; 0.1; FPG SMD=0.04; 95% CI: -0.03; 0.12).

DPP-4 + sulfonylurea vs. sulfonylurea

- The addition of DPP-4 inhibitors to sulfonylurea showed a greater reduction in HbA1c compared with sulfonylurea monotherapy (Figure 6).

Figure 6. Forest plot for meta-analysis of HbA1c change of DPP-4+metformin vs. sulfonylurea+metformin



Conclusions

- **DPP-4 inhibitors added to metformin achieved a better glycemic control compared with metformin monotherapy, with a lower risk of hypoglycemia and without affecting weight versus sulfonylurea and metformin combination.**

References:

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2 DerSimonian L, Laird N. Control Clin Trials. 1986;7:177-88.

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PDB23 ISPOR 17TH ANNUAL EUROPEAN CONGRESS - Amsterdam, November 8th-12th, 2014

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