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REVIEW

Systematic review and meta-analysis of efficacy and safety of combinational therapy with metformin and dipeptidyl peptidase-4 inhibitors

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Abstract Combinational therapies are often required in the management of type 2 diabetes mellitus (T2DM). Among the important candidates, dipeptidyl peptidase-4 inhibitors (DPPIs) and metformin combination (DPPI-MET) have shown promising endeavors. In order to examine the efficacy and safety of such a combination therapy in T2DM patients finding inadequate control with metformin, this systematic review and meta-analysis has been conducted. Literature search was made in multiple electronic databases. Inclusion criteria included; RCTs examining the efficacy and safety of DPPI-MET against placebo-MET or MET-only groups of T2DM patients by observing changes in disease endpoints including HbA1c and FPG, and the length of trial be at least 12 weeks. Mean differences based meta-analyses were performed and heterogeneity assessment was carried out. Nineteen studies were selected and included in the meta-analyses. DPPI-MET significantly improved all disease endpoints and the difference could be noticed up to 2 years in the majority of outcome measures. In comparison with PBO-MET, the DPPI-MET combinational therapy resulted in the percent HbA1c changes from baseline with a mean difference [95% CI] of −0.77 [−0.86, −0.69] in 3-month ($P < 0.00001$), −0.67 [−0.76, −0.59] in 6-month ($P < 0.00001$), −0.67 [−0.88, −0.47] in 1-year ($P < 0.00001$) and −0.36 [−0.53, −0.20] in 2-year trials ($P < 0.0003$). Reduction in body weight and safety profile in the treated and control groups were not different. A combinational therapy with DPPI and metformin significantly improves diabetes clinical indicators and this effect has been observed for up to 2 years herein. Safety and tolerability of DPPI-MET combination have been found well-manageable with a very similar adverse event profile in both treated and control groups.

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Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) prevalence is increasing and this disease could be the seventh leading cause of mortality by 2030. At present, 350 million people are suffering from this devastating disease (WHO, 2013). Microvascular complications associated with diabetes lead to blindness, renal failure and organ loss besides stroke and heart disease related mortality is 2–4 times more in diabetes patients (Green and Feinglos, 2008). It is a progressive disease which often requires multimedication strategy in order to achieve better glycemic control. Lifestyle changes are the prime interventions after the diagnosis of diabetes but metformin is the first line drug to control the disease which may be followed by other drugs such as sulfonylurea, thiazolidinediones and insulin when metformin is found inadequate to control diabetes.

Amongst the add-on treatments, sulfonylurea and thiazolidinediones were studied but because of the higher prevalence of hypoglycemic events and other complications are considered as low priority options. More recent developments in this field include utilization of glucagon like peptide analogues, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPPIs) and sodium-glucose co-transporter-4 inhibitors (SGLTIs) which have potentials to be used as add-on treatments (Ahren, 2008; Nauck et al., 2009a,b; Kurosaki and Ogasawara, 2013).

Whereas, agonists of the glucagon-like peptide-1 (GLP-1) receptor provide pharmacological levels of GLP-1 activity, DPPIs increase concentrations of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the breakdown of these incretins (Drucker and Nauck, 2006; Kendall et al., 2009). Both these incretins improve glucose-dependent insulin release. Meal induced glucagon secretion is also believed to be suppressed by the GLP-1 (Deacon et al., 2004). A number of DPPI drugs have shown efficacy and tolerability potentials and in a meta-analysis of 62 studies, DPPIs as monotherapy were found to decline percent HbA_{1c} by −0.76% when compared to respective placebo or comparator groups (Park et al., 2012).

There is no study so far to meta-analyze the efficacy and safety of the DPPI-metformin combinational therapy against placebo-metformin or metformin only controls. This is important to evaluate this potential combinational therapy as many fixed-dose combinations of metformin and DPPI drugs are proposed and many are in different stages of development. This systematic review and meta-analysis therefore attempts to evaluate the efficacy and safety of the combinational therapy with metformin and DPPIs by examining the data generated from the randomized controlled trials (RCTs) that examined the effectiveness of this combination against placebo-metformin controls in T2DM patients finding metformin therapy inadequate.

2. Methods

2.1. Literature search

Multiple electronic databases were searched for the identification, selection and retrieval of the required research papers. These included Medline/Pubmed, EMBASE, SCOPUS, CINAHL, Google Scholar, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, Cochrane Central Register of Controlled Trials and the ClinicalTrials.gov. Search engines were used with various combinations and phrases of the major MeSH terms including dipeptidyl peptidase-4 inhibitors, sitagliptin, alogliptin, saxagliptin, vildagliptin, linagliptin, dutogliptin, add-on treatment to metformin, combinational therapy, randomized controlled trial, efficacy, safety, tolerability, and diabetes. Lists of references of important articles were also screened for achieving comprehension in the literature search.

2.2. Inclusion and exclusion criteria

This meta-analysis and associated systematic review includes RCTs that examined the efficacy, safety and tolerability of DPPIs in combination with metformin during the years 2000 to September 2013. The participants of these trials were T2DM patients with inadequate control of disease with lifestyle changes and metformin therapy. Primary outcome measures of interest were percent glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), postpandrial glucose (PPG) levels, homeostatic model of assessment (HOMA)-IR (insulin resistance) and -beta (beta cell), proinsulin–insulin ratio (PI), and body weight changes. The inclusion criteria were: (a) RCTs that examined the efficacy and safety of DPPI-MET against PBO-MET or MET-only groups of T2DM patients, (b) the trials had examined the effects of intervention on at least HbA_{1c} and FPG as clinical indicators of disease condition, (c) Disease diagnosis in the participants achieved at least 1 year before the start of the trial and (d) Length of the trial be at least 12 weeks. Exclusion criteria were: (a) RCTs which compared DPPI with metformin as monotherapies, (b) RCTs that studied DPPI-MET against PBO-MET plus other antidiabetic drug/s, (c) RCTs that utilized other contemporary drugs

in combination with metformin as comparators against DPPI-MET, and (d) trials which compared the efficacy and safety of two DPPIs in combination with metformin without a PBO-MET or MET-only group.

2.3. Quality assessment of the trials

The Jadad scale was used to assess the quality of the RCTs included in the meta-analysis (Jadad et al., 1996) which evaluates reports of the RCTs under three major domains: randomization, concealment, and trial success in terms of participant dropout/withdrawal. The scale could award a maximum of 5 points to a RCT if it has (1) carried out randomization, (2) provided details of randomization process in the report, (3) carried out concealment, (4) provided sufficient details of concealment, and (5) provided fate of the participants i.e. dropouts/withdrawals etc. At least 3 out of 5 score was required for a trial to be included in this review. The inclusion of all randomized participants in the final analysis was considered only when at least 75% completeness of follow up was achieved.

2.4. Data extraction, synthesis and statistical analysis

Data regarding participant's demographic, pathological and clinical characteristics, trial design and criteria, interventions, outcome measures and outcomes were collected from research papers published during 2000 and 2013. Data extraction was carried out from textual, tabular and graphic sources as per need and later uniformity of units was ensured by using appropriate calculators.

Meta-analyses were carried out by using Review Manager software (RevMan Version 5.2; Chocrane Collaboration) with the random effects model. In the procedure, means with standard deviation (SD) values were either extracted directly or calculated accordingly that were used as input data for calculating mean differences and confidence intervals of both groups of each study. The overall effect of treatment was based on calculating a weighted average of the inverse variance adjusted individual study effects. Heterogeneity was determined with Chi^2 and I^2 indices and visual examination of funnel plots provided a rough indication of the publication bias.

3. Results

The literature search led to the final selection of nineteen studies after the observance of inclusion and exclusion criteria. A summarized flowchart of the literature search and study selection process has been given in Fig. 1. Table 1 contains the characteristics of these studies. Of the included studies, trial duration was 3 months (3 trials), 6 months (12 trials), 1 year (3 trials) and 2 years (1 trial). The DPPIs studied were SITA (7 trials), VILDA (4 trials), SAXA (3 trials), LINA (3 trials) and ALO (2 trials). All of these trials used changes in percent HbA1c as the primary outcome measure.

Overall, the population size of this meta-analysis is 12180 T2DM patients with inadequate control on the disease with lifestyle interventions and metformin. Among the salient demographic features, the age of the participants was 54.86 ± 10.01 (mean ± SD), 52.4% of the participants were males and duration of disease since diagnosis was 5.15 ± 4.13 years (mean ± SD; range 1.7 ± 3 to 7 ± 6.3). Important clinical indicators of this sample of T2DM patients were: HbA1c (8.3 ± 0.82), FPG (9.93 ± 2.4) and BMI (30.12 ± 4.9).

The quality of the included studies was generally good with almost all studies scored 4/5 on Jadad scale. Sixteen studies also mentioned the accordance of their study protocols with the Helsinki Declaration of good practices.

A relatively higher level of heterogeneity was observed in many comparisons but not all and in many cases, there was no heterogeneity at all (I^2 ranged from 0% to 85%). A sensitivity analysis by making comparisons with either high dose groups or low dose groups did not give significant difference in the results achieved from the overall meta-analyses in the over efficacy parameters as well as in heterogeneity assessment. Publication bias was also evident from the observation of the funnel plots of almost all parameters and their categories (Fig. 2).

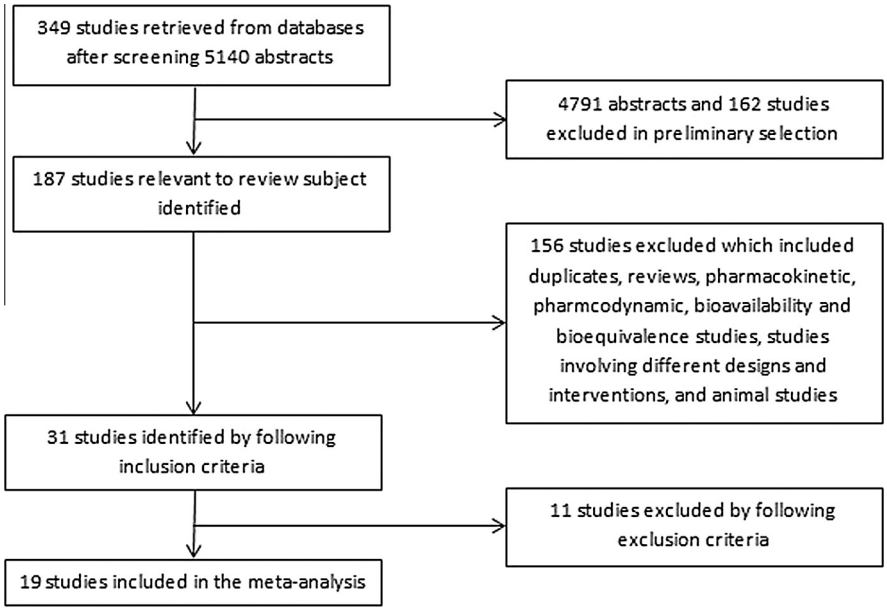


Figure 1 Flowchart of study retrieval and selection procedure.

Table 1 Characteristics of the studies included in the systematic review and meta-analyses.

Study/drug/duration	Participants	Participant's characteristics	Clinical indicators	Outcome measures	Outcomes	Limitations
Ahren et al. (2004, 2005)/VILDA/ 52 week	Patients: 57 (31 VILDA vs 26 Placebo)	Age: 56.7 ± 9.6 Males: 77% BMI: 29.55 ± 3.55 T2DM length: 5.55 ± 3.95	HbA1c (%): 7.7 ± 0.6 FPG (mmol/L): 9.85 ± 1.75 MET dosage: 1500–3000 mg/d	Beta-cell function, postmeal insulin sensitivity, HbA1c, FPG	Improved beta-cell function and postmeal insulin sensitivity and significant reduction in HbA1c and FPG after DPPI-MET treatment	Small population size
Bergenstal et al. (2012)/SITA/ 52 week	Patients: 636 (SITA 177, Placebo 90, Taspoglutide 10 mg 182 and 20 mg 187)	Age: 55.95 ± 9.6 Males: 55.66% BMI: 32.47 ± 5.3 T2DM length: 5.8 ± 4.6	HbA1c (%): 7.97 ± 0.86 FPG (mmol/L): 9.61 ± 2.56 MET dosage: ⩾ 1,500 mg/d	Primary: HbA1c Secondary: % patients achieving HbA1c ⩽6.5% and ⩽7%, FPG, BW	Greater reductions in HbA1c, FPG and BW in taspoglutide group that SITA group. Both significantly better than placebo	Placebo group maintained by 24th week only.
Bosi et al. (2007)/ VILDA/24 week NCT00099892	Patients: 544 (VILDA 50 mg 177, 100 mg 185 and Placebo 182)	Age: 54.2 ± 9.83 Males: 57% BMI: 32.6 ± 5.5 T2DM length: 6.3 ± 5.16	HbA1c (%): 8.4 ± 1.0 FPG (mmol/L): 9.9 ± 2.4 MET dosage: 2109 ± 315 mg/d	HbA1c, FPG and BW	VILDA significantly reduced HbA1c and FPG	
Charbonnel et al. (2006)/SITA/ 24 week NCT0086515	Patients: 701 (237 SITA and 464 placebo groups).	Age: 54.55 ± 10 Males: 58% BMI: 31.2 ± 5.1 T2DM length: 6.3 ± 5.25	HbA1c (%): 8 ± 0.8 FPG (mmol/L): 9.55 ± 2.3 MET dosage: > 1500 mg/d	Primary: HbA1c Secondary: FPG, glucose, insulin, and C-peptide.	Significant reductions in HbA1C, FPG, and 2-h postmeal glucose	Small study duration
DeFronzo et al. (2008)/SAXA/ 24 week NCT00121667	Patients: 743 (SAXA-MET 2.5 mg = 192, 5 mg = 191, 10 mg = 181) and PBO-MET = 179)	Age: 60 ± 9 Males: 58% BMI: 31.9 ± 4.3 T2DM length: 6.5 ± 5.2	HbA1c (%): 8 ± 0.5 FPG (mmol/L): 9.75 ± 2.6 MET dosage: 1,500 and ⩽ 2,550 mg/day	Primary: HbA1c Secondary: FPG, 2-h PPG, % pts achieving HbA1c ⩽ 7%, HOMA.	Significant reductions in HbA1c, FPG, PPG etc. in DPPI-MET compared to PBO-MET	
Forst et al. (2010)/ LINA/12 week NCT00309608	Patients: 333 (LINA 1 mg 65, 5 mg 66 and 10 mg 66, glimipride 65 and placebo 71)	Age: 54.6 ± 10 Males: 51% BMI: 31.4 ± 4.8 T2DM length: 7 ± 6.3	HbA1c (%): 8.3 ± 0.8 FPG (mmol/L): 10.3 ± 2.3 MET dosage: ⩾ 1500 mg/day	Primary: HbA1c Secondary: FPG, 2-h PPG, % pts achieving HbA1c ⩽ 7%, HOMA.	Significant reductions in HbA1c and FPG levels in LINA-MET groups	Small study duration
Goldstein et al. (2007)/SITA / 24 week; Williams-Herman et al., 2009 (2010)/54 week & 104 week NCT00103857	Patients: 1091 (182 SITA 50 mg-MET 2 g, 190 SITA 50 mg–MET 1 g, 179 SITA 100 mg, 182 MET 1 g, 182 MET 500 mg and 176 placebo groups).	Age: 53.3 ± 9.93 Males: 49% BMI: 32 ± 6.63 T2DM length: 4.46 ± 4.45	HbA1c (%): 8.78 ± 0.95 FPG (mmol/L): 11.1 ± 2.7 MET dosage: 1000 mg/d vs 2000 mg/d	HbA1c, FPG, 2-h PPG, FSI, FSP, proinsulin/ insulin ratio, HOMA, lipids and BW.	Substantial and additive glycemic control that was well tolerated. Significant reduction in HbA1c, FPG and 2-h PPG	Randomization was carried out initially for 24 week trial that was extended beyond for 54 and 104 weeks.
Goodman et al. (2009)/VILDA/ 24 week NCT00351884	Patients: 370 (VILD 248 and PBO 122)	Age: 54.7 ± 10.4 Males: 54% BMI: 31.5 ± 4.2 T2DM length: 4.46 ± 4.45	HbA1c (%): 8.6 ± 1.1 FPG (mmol/L): 11 ± 2.8 MET dosage: 1880 ± 380 mg/d vs 1932 ± 410 mg/d	Primary: HbA1c Secondary: FPG	Significant reductions in HbA1c, FPG but no difference in BW	

Haak et al. (2012)/ LINA/24 week NCT00798161	791 (LINA 5 mg = 142, MET 500 mg BID = 144, MET 1 g BID = 147, LINA 2.5 mg + MET500 mg BID = 143, LINA 2.5 mg + MET 1 g BID = 143, PBO = 72)	Age: 55.3 ± 10.8 Males: 53.5% BMI: 29.1 ± 5.1 T2DM duration: 64% over 1 year wth 38% since 1–5 years	HbA1c (%): 8.66 ± 0.97 FPG (mmol/L): 10.88 ± 2.7 MET dosage: 1000 to 2000 mg/day	Primary: HbA1c Secondary: FPG	Initial LINA-MET therapy was superior to MET alone in improving glycemic Control. A similar safety and tolerability profile, no weight gain and a low risk of hypoglycemia was observed	About half of the population was not treatment-naïve.
Jadzinsky et al. (2009)/ SAXA/24 week NCT00327015	Patients: 1306 (SAXA-MET 5 mg = 320, 10 mg = 323), SAXA 10 mg = 335 and MET = 328 Intake: Before morning meal	Age: 52.1 ± 11.7 Males: 49% BMI: 30.2 ± 4.8 T2DM duration: 1.7 ± 3	HbA1c (%): 9.5 ± 1.2 FPG (mmol/L): 11.2 ± 3.1 MET dosage: 1 g to 2 g per day	Primary: HbA1c Secondary: FPG, % pts achieving HbA1c $\leqslant$ 7%, HOMA, AUC PPG etc.	Significant reductions in HbA1c and FPG in DPPI-MET compared to PBO-MET	Slightly biased design to study adverse events in comparing groups because of mean exposure time differences.
Nauck et al. (2009a,b)/ ALO/26 week NCT00286442	Patients: 527 (213 ALO 12.5 mg, 210 ALO 25 mg and 104 placebo groups).	Age: 55 ± 11 Males: 50% BMI: 32 ± 5.3 T2DM length: 6 ± 5	HbA1c (%): 7.96 ± 0.8 FPG (mmol/L): 9.6 ± 2.6 MET dosage: < 1.5 g: 9.2 ± 16.3, 1.5–2 g: 70.4 ± 123 and > 2 g: 20.6 ± 36.3	Primary: HbA1c Secondary: FPG	Significant reductions in HbA1c and FPG levels seen	Small study duration
Olansky et al. (2011) / SITA /44 week NCT00482729	Patients: 1250 (625 SITA and 621 MET monotherapy groups).	Age: 49.7 y Males: 56.5% BMI: 33.35 T2DM length: 3.35 y	HbA1c (%): 9.1 ± 1.3 FPG (mmol/L): 10.7 ± 3.2 MET dosage: 1000–2000 mg/day	Primary: HbA1c Secondary: FPG, blood lipid profile, body weight	Significant reductions in HbA1c, FPG but no difference in BW	Patients were allowed to use additional antihypertensives but patients were not appraised bout this and not paid.
Pan et al. (2012)/ VILDA/24 week NCT00822211	438 (VILDA 50 mg QD = 148, 50 mg BID = 146 ad PBO = 144)	Age: 54.1 ± 9.9 Males: 46.8% BMI: 25.5 ± 3.2 T2DM length: 5.2 ± 4.65	HbA1c: 8.06 ± 0.84 FPG (mmol/L): 8.76 ± 2.05 MET dosage: > 1500 mg/day	Primary: HbA1c Secondary: FPG	Significant reductions in HbA1c, FPG	
Raz et al. (2008)/SITA/ 30 week NCT00337610	Patients: 190 (96 SITA and 94 placebo)	Age: 54.85 ± 9.5 Males: 49% BMI: 30.25 ± 3.16 T2DM length: 5.02 ± 4.6	HbA1c (%): 8.7 ± 0.84 FPG (mmol/L): 11.1 ± 2.07 MET dosage: > 1500 mg/day	Primary: HbA1c Secondary: FPG, PPG, FSI, HOMA, lipids	Significant reductions in HbA1c, FPG, 2-h PPG, HOMA-β	Inclusion of patients with restricted severity. Relatively small study duration
Ross et al. (2012)/LINA/ 12 week with extension period NCT01012037	Participants: 491 (LINA 2.5 mg BID = 223, 5 mg QD = 224 and PBO = 44)	Age: 58.6 ± 10.3 Males: 57% BMI: 29.6 ± 5.1 T2Dm duration: 4.9 ± 3.6	HbA1c (%): 7.97 ± 0.75 FPG (mmol/L): 9.17 ± 2.11	Primary: HbA1c Secondary: FPG	Significant reductions in HbA1c, FPG	Small study duration
Scott et al. (2008)/SITA/ 18 week NCT00541775	Patients: 271 (SITA 94, rosiglitazone 87 and placebo 92)	Age: 55.1 ± 9.8 Males: 59% BMI: 30.2 ± 4.9 T2Dm duration: 4.9 ± 3.6	HbA1c (%): 7.7 ± 0.9 FPG (mmol/L): 8.78 ± 1.8 MET dosage: $\geqslant$ 1500 mg/day	HbA1c, FPG, FSI, FSP, PI/I ratio, HOMA, lipids.	Significant reductions in HbA1c, FPG, 2-h PPG, HOMA-β	Small study duration

(*continued on next page*)

Table 1 (*continued*)

Study/drug/duration	Participants	Participant's characteristics	Clinical indicators	Outcome measures	Outcomes	Limitations
Seino et al. (2012)/ALO/12 week NCT01318109	Patients: 288 (ALO 12.5 mg = 92, 25 mg = 96 and MET only = 100)	Age: 52.6 ± 8.28 Males: 69% BMI: 25.85 ± 4.14 T2Dm duration: 6.33 ± 4.84	HbA1c (%): 7.97 ± 0.8 Fasting C-peptide (ng/L): 1.84 ± 0.82 MET dosage: 500–750 mg/day	HbA1c, FPG, PPG	Significant reductions in % HbA1c and FPG levels	
Taskinen et al. (2011)/LINA/24 week NCT00601 250	Participants: 701 (LINA 5 mg = 523 and PBO = 177)	Age: 56.5 ± 10.3 Males: 54% BMI: 29.9 ± 4.88 T2Dm duration: 89% with over 1 year	HbA1c (%): 8.08 ± 0.87 FPG (mmol/L): 9.4 ± 2.4	Primary: HbA1c Secondary: FPG, PPG, FSI, HOMA, lipids	Significant reductions in HbA1c, FPG, 2-h PPG, HOMA-β	
Yang et al. (2012)/SITA/24 week NCT00813995	Participants: 395 (SITA 197, PBO 198)	Age: 54.6 ± 9.4 Males: 50.6%	HbA1c (%): 8.5 ± 0.9 FPG (mmol/L): 9.65 ± 2.2 MET dosage: 1000–1700 mg/day	HbA1c, FPG, PPG	Significant reductions in % HbA1c, FPG, and PPG	Participants switched over from multiple antidiabetic drugs after a washout period to LINA-MET trial
Yang et al. (2011)/SAXA/24 week NCT00661362	570 (SAXA-MET 283 and PBO-MET 287)	Age: 54.6 ± 10.24 Males: 48.26%	MET dosage: > 1500 mg/day	HbA1c, FPG, PPG	Significant reductions in % HbA1c, FPG, and PPG	

The major findings of the meta-analyses are presented in Table 2. In comparison with PBO-MET, the DPPI-MET combinational therapy resulted in the percent HbA_{1c} changes from baseline with a mean difference [95% CI] of −0.77 [−0.86, −0.69] in 3-month ($P < 0.00001$), −0.67 [−0.76, −0.59] in 6-month ($P < 0.00001$), −0.67 [−0.88, −0.47] in 1-year ($P < 0.00001$) and −0.36 [−0.53, −0.20] in 2-year trials ($P < 0.0003$). Heterogeneity as estimated by I^2 was 67% and 78% in 6-month and 1-year trials respectively (Fig. 3).

Fasting plasma glucose also declined and the mean difference from baseline between DPPI-MET and PBO-MET along with [95% CI] was −1.46 [−2.0, −0.91] in 3 months ($P < 0.00001$), −1.09 [−1.23, −0.95] in 6 months ($P < 0.00001$), −0.74 [−1.00, −0.49] after 1 year ($P < 0.00001$) and −0.58 [−1.01, −0.15] after 2 years ($P < 0.005$). Heterogeneity as estimated by I^2 was 85%, 46% and 14% in 3-month and 6-month and 2-year trials respectively. However, a sensitivity analysis (exclusion of Forst et al., 2010) left heterogeneity at 0% in the comparison of 3-month trials.

The differences between DPPI-MET and PBO-MET with regard to changes from baseline in reducing PPG levels were also pronounced. The mean difference [95% CI]) was −2.46 [−2.92, −2.0] after 3–6 month ($P < 0.00001$), −1.74 [−2.28, −1.19] after 1 year ($P < 0.00001$) and −1.29 [−1.98, −0.61] after 2 year ($P < 0.006$) trials. Heterogeneity (I^2) was 71% in the 3–6 month trials.

The differences between DPPI-MET and PBO-MET with regard to changes from baseline in proinsulin:insulin ratio were significant in up to 1 year trials but not in a 2 year trial. The mean difference [95% CI]) was −0.05 [−0.08, −0.01] after 3–6 month ($P < 0.0008$), −0.05 [−0.08, −0.02] after 1 year ($P < 0.005$) and −0.03 [−0.08, 0.02] after 2 year ($P = 0.28$) trials. Heterogeneity (I^2) was 57% in the 3–6 month trials and not apparent in other categories.

The differences between DPPI-MET and PBO-MET with regard to changes from baseline in HOMA-beta were significant throughout up to 2-year trials. The mean difference [95% CI]) was 12.6 [9.1, 16.09] after 3–6 month ($P < 0.00001$), 24.7 [15.62, 33.73] after 1 year ($P < 0.00001$) and 21.2 [6.72, 35.72] after 2 years ($P < 0.003$). Heterogeneity (I^2) was 53% in the 3–6 month trials, and 14% in a 2-year trial.

The mean difference [95% CI]) between DPPI-MET and PBO-MET in changes from baseline in HOMA-IR was −0.4 [−0.79, −0.0] after 3–6 month ($P < 0.05$), 1.47 [1.25, 4.18] after 1 year ($P < 0.00001$) and 0.46 [−0.37, 1.29] after 2 years ($P = 0.28$). Heterogeneity (I^2) was 46% in the 3–6-month trials, and 96% in a 1-year trial.

The safety profile of the DPPIs synthesized by averaging the data of the included studies was very similar in both treated and control groups (Table 3). The percentage of patients encountering at least one serious AE was 2.7 and 2.7 and discontinuation due to any AE was 2.9 and 2.1 in the DPPI-MET and PBO-MET groups respectively.

The effect of DPPI-MET on clinically important physiological indicators was reported to be neutral by the majority of studies. A synthesis based on averaging the effects on lipid profile mentioned by five studies as DPPI-MET vs PBO-MET was total cholesterol (1.83 vs 4.43), triglyceride (−1.7 vs 7), high-density lipoprotein cholesterol; HDL-C (3.87 vs 4.05), low-density lipoprotein cholesterol (3.8 vs 5.57), and non-HDL-C (1.67 vs 5.77). These values are percent change from baseline.

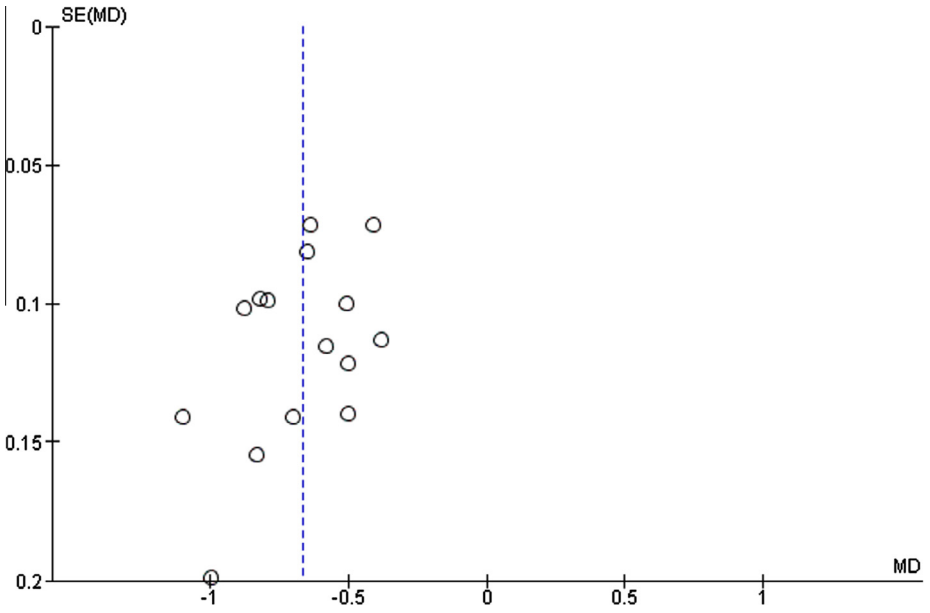


Figure 2 Funnel plot reflecting low-level publication bias in the meta-analysis of DPPI-MET vs PBO-MET for evaluating the mean difference in changes from baseline in percent HbA1c.

4. Discussion

This study finds a significant beneficial effect of the combinational therapy with DPPI and metformin for T2DM patients when compared to the placebo-metformin combination or only metformin. All major endpoints such as HbA_{1c}, FPG, PPG, PI and HOMA (-beta and -IR) exhibited statistically significant improvements which in the majority of cases persisted up to 2 years. The maintenance of these endpoints at target levels along with safety and tolerability is highly desirable in T2DM management.

Although, the improvements in HbA1c, FPG and PPG were more pronounced in the trials of up to 1 year duration they were relatively less in the trials of longer duration. Reductions in the mean difference in the changes from baseline between treated and control groups for these endpoints from 3-month trials to 2-year trial were −0.77 to −0.36 for percent HbA1c, from −1.46 to −0.58 ng/ml for FPG and from −2.46 to −1.29 ng/ml for PPG. However, reduction in significance levels was also associated with the number of trials which was higher in short-term trials and on the other only one trial could be included in the analysis of 2 years long treatment effect.

In this meta-analysis, PI significantly reduced in 3–6 months and 1 year trials (by 0.5 in both durations) but the mean difference (0.3) between treated and control groups was not significant in the 2-year trial. Improvement in HOMA-beta and HOMA-IR was significantly better in DPPI-MET groups but the mean differences of changes from baseline in trials of different durations were not uniform (Table 1). However, in these cases (PI and HOMA), analysis for over 6 month duration was based on the least number of eligible trials.

Reports of long-term effectiveness of DPPIs are less available as compared to 6-month and 1-year trials. Whereas a 2 year long trial which compared SITA-MET and MET-only found change from baseline in HbA_{1c} of −1.7% in the former and −1.3% in the latter groups (Williams-Herman et al., 2010), a comparable RCT (Seck et al., 2010) which compared SITA-MET with glipizide-MET reported a least squares mean change in HbA_{1c} of −0.54% from baseline in the SITA-MET group after 2 years of treatment. In this trial body weight declined up to −1.6 kg in the SITA-MET group from baseline whereas in the trial of Williams-Herman et al. (2010) after 104 weeks, body weight reduction was noted up to −1.2 kg in SITA-MET group and −2.4 kg in MET-only group. So far, the efficacy and safety of SAXA-MET have been reported for up to 3 years (Rosenstock et al., 2013).

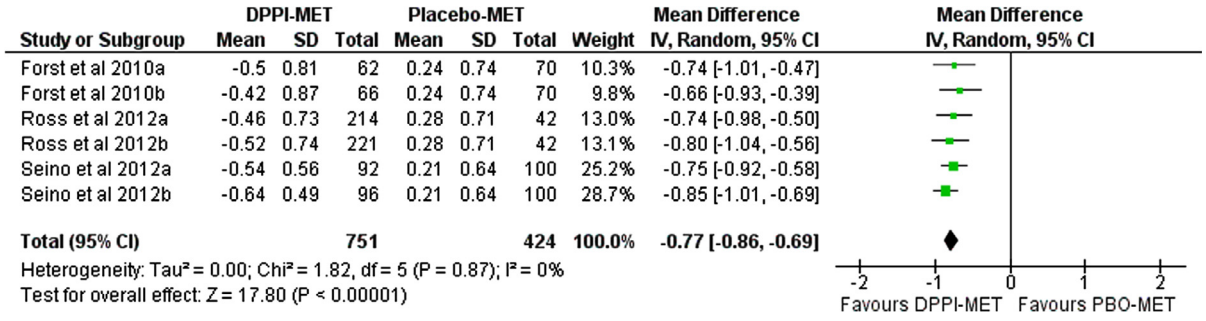
Generally, DPPIs are considered as weight-neutral medication for T2DM (Inzucchi et al., 2012). In the present review, the effect size of body weight reduction from baseline in 6-month trials has been noticed as −0.6 (range, −0.1 to −1.6) kg and −0.8 (range, −0.2 to −1.6) kg in DPPI-MET and PBO-MET groups respectively. One year long trials have noticed changes in body weight from baseline as −1.1 kg in SITA-MET and −1.2 kg in MET-only group (Olansky et al., 2011), up to −1.7 kg in SITA-MET group and −1.5 kg in MET-only groups (Williams-Herman et al., 2009) and −0.2 kg in both VILDA-MET and PBO-MET groups (Ahren et al., 2005). Goodman et al. (2009) noted no reduction in body weight of VILDA-MET treated patients against 0.69 kg reduction in PBO-MET group. Raz et al. (2008) also found no meaningful between-group (SITA-MET vs PBO-MET) difference in body weight change in a 30-week trial. However, DeFronzo et al. (2008)have noted an inverse relationship between increasing doses of SAXA-MET and mean changes from baseline in body weight (−1.43, −0.87, and −0.53 kg for 2.5, 5, and 10 mg) at week 24 of treatment.

The contemporaneous of DPPI-MET is not yet fully clear as some other drugs have shown comparable efficacy and safety properties in RCTs. The GLP-1 receptor analogues (GLPA) such as liraglutide and exenatide have been found to be superior when co-administered with metformin with a mean difference of 0.53% between DPPI-MET and GLPA-MET in declining

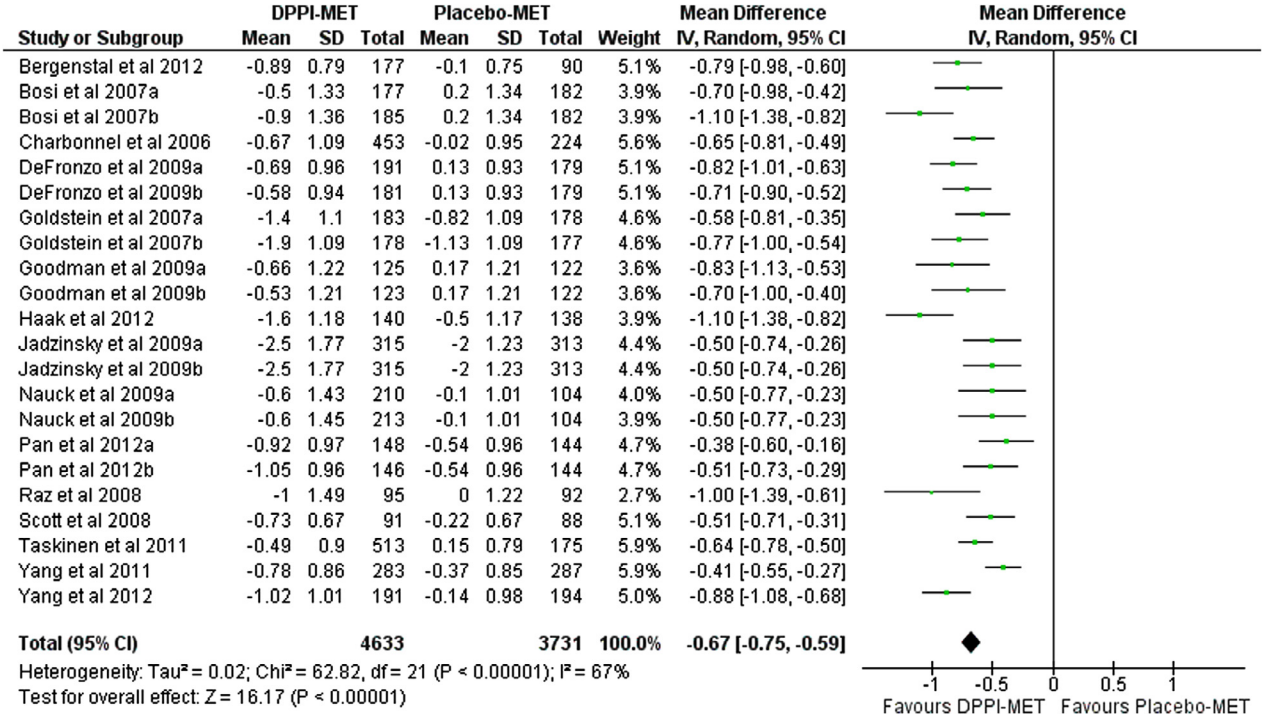
Table 2 Major findings of the meta-analysis.

Parameter/ duration	Study groups	Participants	Change from baseline (mean ± SD)		Mean difference [95% CI]	Significance level	Heterogeneity (I^2) (%)
			SGLTI	Placebo			
HbA1c							
After 3 months	6	1175	−0.5 ± 0.7	0.24 ± 0.7	−0.77 [−0.86, −0.69]	$P < 0.00001$	0
After 6 months	22	8364	−0.85 ± 0.1	−0.19 ± 0.9	−0.67 [−0.76, −0.59]	$P < 0.00001$	67
After 1 year	6	2125	−1.15 ± 1	−0.47 ± 1	−0.67 [−0.88, −0.47]	$P < 0.00001$	78
After 2 years	2	352	−1.6 ± 0.9	−1.2 ± 0.8	−0.36 [−0.53, −0.20]	$P < 0.0001$	0
FPG							
After 3 months	6	1148	−1.3 ± 1.67	0.16 ± 1.66	−1.46 [−2.0, −0.91]	$P < 0.00001$	85
After 6 months	22	8335	−1 ± 2.2	0 ± 2.25	−1.09 [−1.23, −0.95]	$P < 0.00001$	46
After 1 year	4	1735	−2.4 ± 2.3	−1.6 ± 2.46	−0.74 [−1.00, −0.49]	$P < 0.00001$	0
After 2 years	2	351	−2.9 ± 2.3	−1.62 ± 2.4	−0.58 [−1.01, −0.15]	$P < 0.005$	14
PPG							
After 3–6 months	14	3665	−2.5 ± 3.37	−0.2 ± 3.2	−2.46 [−2.92, −2.0]	$P < 0.00001$	71
After 1 year	2	461	−5.99 ± 3	−4.24 ± 3	−1.74 [−2.28, −1.19]	$P < 0.00001$	0
After 2 years	2	284	−6.1 ± 2.9	−4.8 ± 2.9	−1.29 [−1.98, −0.61]	$P < 0.006$	0
Proinsulin/insulin ratio							
After 3–6 months	9	1990	−0.2 ± 0.36	−0.1 ± 0.42	−0.05 [−0.08, −0.01]	$P = 0.0007$	57
After 1 year	2	419	−0.2 ± 0.83	−0.1 ± 0.9	−0.05 [−0.08, −0.02]	$P < 0.005$	0
After 2 years	2	233	−0.19 ± 0.8	−0.16 ± 0.2	−0.03 [−0.08, 0.02]	$P = 0.28$	0
HOMA-beta							
After 3–6 months	9	3040	12 ± 34.7	0 ± 35.4	12.6 [9.10, 16.09]	$P < 0.00001$	53
After 1 year	2	504	38.3 ± 52	13.6 ± 51.5	24.7 [15.62, 33.73]	$P < 0.00001$	0
After 2 years	2	316	47.4 ± 60	27 ± 60	21.2 [6.72, 35.72]	$P < 0.003$	14
HOMA-IR							
After 3–6 months	9	1906	−0.8 ± 2.86	−0.5 ± 2.87	−0.4 [−0.79, −0.00]	$P < 0.05$	46
After 1 year	3	561	−1.37 ± 2.8	−2.83 ± 3.4	1.47 [1.25, 4.18]	$P < 0.00001$	96
After 2 years	2	316	−1.3 ± 3.66	−1.75 ± 3.7	0.46 [−0.37, 1.29]	$P = 0.28$	0

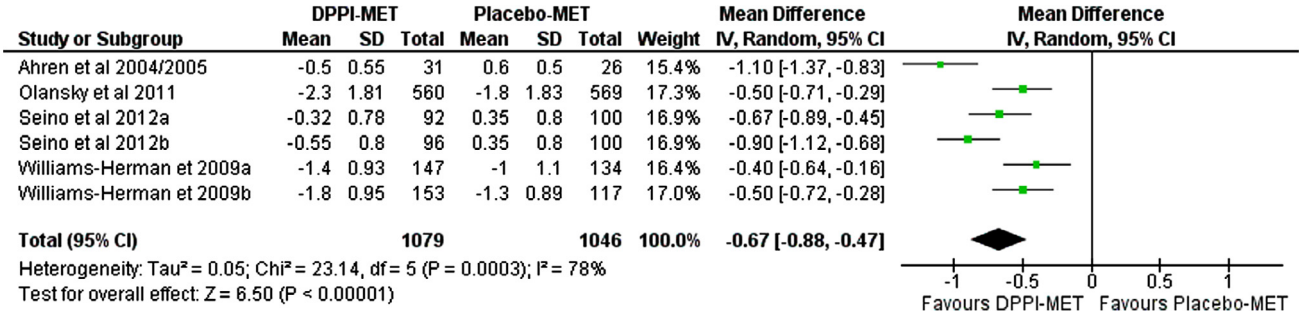
Weighted mean difference [95% CI].



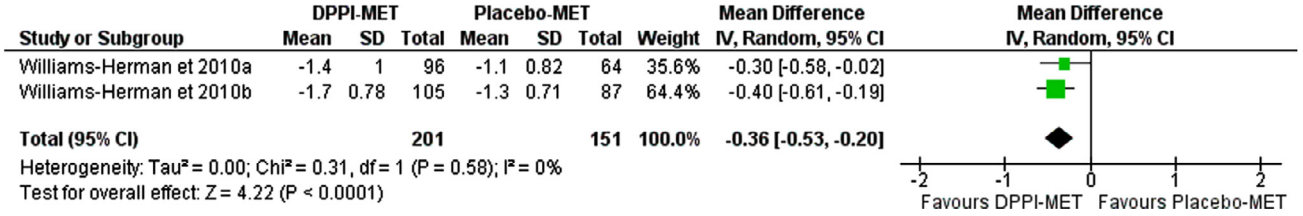
(A)



(B)



(C)



(D)

Figure 3 Efficacy of DPPI-MET combinational therapy in declining percent HbA1c in trials of various durations; (A) 3-month, (B) 6-month, (C) 1-year, and (D) 2-year. Please note that, keeping in view the similar effects of different doses, two doses of some studies are included in the analyses as sensitivity analyses did not note much difference. Study identification has been indicated as a/b and dosage details are presented in Table 1.

Table 3 Prevalence of adverse events in the included studies*.

Adverse events (AE)	C	T
At least one AE	56.0	56.3
At least one drug-related AE	11.9	12.5
At least one serious AE	2.7	2.9
Discontinuation due to AE	2.7	2.1
Back pain	3.1	2.2
Influenza	3.4	3.2
Abdominal pain	2.8	2
Arthralgia	2.4	1.5
Nausea	3.5	3.6
Vomiting	1.4	1.8
Diarrhea	5.7	5.8
Constipation	1.7	1.6
Gastrointestinal	15.7	17.7
Urinary tract infection	3.6	4
Pain in extremity	3.9	3
Headache	3.4	4.8
Nasopharyngitis	6.9	7.1
Respiratory tract infection	2.9	2.2
Hypoglycemia	2.8	2.1
Hypertension	3.6	3.4

* Only those AEs are included which are mentioned by at least five studies.

HbA_{1c} (Pratley et al., 2010, 2011; Bergenstal et al., 2012). A similar finding has also been reported by Aroda et al. (2012) who compared DPPIs with GLPAs in a meta-analysis and found a superiority of GLPAs of about 0.5% in declining HbA_{1c}. One RCT which compared SGLTI-MET with DPPI-MET found the former combination better in declining percent HbA_{1c} with a mean difference of 0.37% between canagliflozin-MET and SITA-MET (Schernthaner et al., 2013). DPPI-MET therapy has also been suggested to be upper hand to metformin up-titration because of low gastrointestinal side effects in the former intervention (Filozof et al., 2010; Hermans et al., 2012).

Lesser availability of longer duration RCTs for this study was an important limitation which might be overcome to some extent in coming years when the results of some ongoing trials will be available. Higher levels of statistical heterogeneity observed in many comparisons may also be considered as a limitation. Sensitivity analyses could reduce heterogeneity significantly at least in one comparison in which I^2 declined from 85% to 0% when a single trial was excluded (see para 6 of Section 3). To which extent it was attributable to clinical and methodological heterogeneity could not be elucidated. However, the age of the participant population deviated 10 years from the mean (54) and mean duration of disease since diagnosis was 5.15 with a standard deviation of 4.13 and range of 1.7–7.0 years. Furthermore BMI deviated about 5 from a mean of 30, though relatively smaller deviations were noted for major clinical indicators. In multi-center and multi-national trials ethnicity may also contribute to overall heterogeneity.

5. Conclusion

A combinational therapy with DPPI and metformin significantly improves diabetes clinical indicators. This study has observed the persistence of effect for up to 2 years but the efficacy of DPPI-MET combination therapy has been reported beyond this period. Analysis of the body weight effect of this combination revealed that DDPIs are weight neutral drugs and slight decrease in body weight because of this therapy was attributable to metformin. Safety and tolerability of this combinational therapy have been found well-manageable with a very similar adverse event profile in both treated and control groups. Therefore, this study finds that combinational therapy with a DPPI and metformin is a valuable strategy especially as second line therapeutic option, however, availability of more data in a few years will clarify the position of DPPIs in the armamentarium against diabetes and possibly more specific prescription.

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