Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: Systematic review and meta-analyses

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A R T I C L E   I N F O

Article history:
Received 27 September 2013
Received in revised form 7 February 2014
Accepted 15 June 2014
Available online 22 June 2014

Keywords:
Metformin
Childhood obesity
Diabetes mellitus
Body mass index
Insulin sensitivity

A B S T R A C T

Aims: In search of add-on treatments to metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitors are potential candidates. This meta-analysis examines the potential use of SGLT-2 inhibitors in combination with metformin as a therapeutic option for type 2 diabetes management in patients with inadequate control with metformin.

Methods: A literature search was made in several databases for randomized controlled trials (RCTs) utilizing metformin therapy combined with SGLT-2 inhibitors or placebo. Heterogeneity was estimated with I² statistics and random effect model was chosen for the meta-analyses of mean differences in changes from baseline in both SGLT-2 inhibitor treated and control groups.

Results: Seven RCTs were selected for the meta-analysis. In comparison with placebo-MET, the SGLT-2 inhibitor–MET combination therapy resulted in significant HbA1c decline in 12–24 week duration, to less extent after 1 year (−0.37 [−0.77, 0.03]; P = 0.07) but not by 2 year (−0.41 [−1.09, 0.28]; P = 0.24) duration. SGLT-2 inhibitor–MET significantly lowered FPG and body weight after 24 weeks, 1 year, and 2 years. Systolic and diastolic blood pressure declined only in the short-term (12–24 weeks). After 2 years, neither systolic (−1.80 [−6.18, 2.58]; P = 0.42) nor diastolic blood pressure (−0.20 [−2.94, 2.54]; P = 0.89) declined significantly more than control. Incidence of suspected genital infections was slightly more in SGLT-2 inhibitor–MET group.

Conclusion: SGLT-2 inhibition in combination with metformin is a potential therapeutic option based on its effects on glycemic control, body weight, and blood pressure, but further trials are required to refine this evidence.

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1. Introduction

Type 2 diabetes mellitus (T2DM) poses increased risk of morbidity and mortality, and is associated with reduced life expectancy of up to 12–13 years [1]. In spite of the developments in diabetes management, the prevalence of this disease is increasing [2]. Because of its progressive nature, therapeutic shifts and intensifications are often required to reduce the risk of glucotoxicity while avoiding serious side effects. In the initial
phases, lifestyle interventions, focusing on diet and physical exercise, are the most important recommendations, but the majority of patients require medication as well. Metformin is the first line drug which effectively provided glycemic control, increases insulin sensitivity and improves body weight. However, it is often observed that metformin becomes inadequate to control T2DM at some stage and thus requires add-on treatments. Among the potential candidates for supplementing metformin’s efficacy, insulin secretagogues such as sulphonylurea and insulin sensitizers such as thiazolidinediones are less popular because of low-profile glycemic durability, increased hypoglycemic events’ occurrence and negative effects on body weight. However, many recent developments in T2DM therapeutics have paved the path for improving management with drugs including sodium-glucose co-transporter (SGLT) inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase inhibitors and glucagon like peptide analogs [3,4].

Many drugs are found to selectively and reversibly inhibit SGLTs and thus lower blood glucose levels by inducing glucosuria with a urinary loss of approximately 200–300 kcal/day regardless of insulin status. Besides providing better glycemic control, these agents are also found to manifest favorable effects on blood pressure and body weight. SGLT-1 and SGLT-2 are important targets of this response. The SGLT-1 is a low-capacity and high-affinity protein expressed mainly in the small intestine and late proximal renal tubules. However, its overall contribution to glycemic control is limited as it is involved in intestinal absorption of sugars such as glucose and galactose. The SGLT-2 is a high-capacity and low-affinity protein abundantly expressed in the initial proximal renal tubules and plays the most important role in reabsorbing 80–90% of glucose [1,5,6]. So far, dapagliflozin, ipragliflozin, canagliflozin, empagliflozin, tofagliflozin, and luseogliflozin are SGLT-2 inhibiting drugs which are being studied extensively for their therapeutic potential in T2DM [7].

A number of studies have evaluated the pharmacokinetics and pharmacodynamics of SGLT-2 inhibitors in healthy subjects [8–10] as well as in T2DM [11–13]. Trials to study the efficacy and safety of the SGLT-2 inhibitors in T2DM involve varying designs from monotherapy comparisons to multi-therapy studies [14–30]. Some aspects of therapies involving SGLT-2 inhibitors have also been reviewed systematically [31,32]. One important area of research is the evaluation of the potential of SGLT-2 inhibitors to overcome metformin inadequacy. Some reports of randomized controlled trials (RCTs) are now available. The present study systematically reviews this important aspect of T2DM management and performs a meta-analysis of RCTs in order to assess various parameters of SGLT-2 inhibitor efficacy and safety when added to ongoing metformin therapy.

2. Method

2.1. Literature search

A literature search was made for research papers published between 2000 and January 2014 in Medline/Pubmed, Embase, Scopus, Web of Science databases including Science Citation Index Expanded, Conference Proceedings Citation Index-Science, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov databases. Major MeSH terms used were: type 2 diabetes mellitus, metformin, add-on treatment, sodium-glucose cotransporters-2, dapagliflozin (DAPA), ipragliflozin (IPRA), canagliflozin (CAN), tofagliflozin (TOFO), empagliflozin (EMPA), and luseogliflozin (LUSEO), efficacy, safety, tolerability, etc. These terms were used in different combinations and phrases. All the selected research articles obtained from the literature search were also explored for cross-references.

2.2. Inclusion and exclusion criteria

The studies that evaluated the efficacy, safety, and tolerability of SGLT-2 inhibitors in combination with metformin (hereinafter SGLT-2 inhibitor–MET) by comparing with placebo-controlled or metformin-only (hereinafter placebo-MET) groups are included in this analytical review. To assess parametric efficacy, outcome measures selected were: changes from baseline in percent glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) levels in millimole/liter (mM/L), body weight (BW) in kilograms (kg), and systolic and diastolic blood pressure (SBP and DBP) in millimeter mercury (mmHg).

Following criteria were used for the screening and subsequent selection of the studies. The inclusion criteria were: (a) RCTs recruiting T2DM patients in order to evaluate the efficacy and safety of SGLT-2 inhibitor/s in combination with metformin; (b) the trial had examined the SGLT-2 inhibitor by using a placebo-controlled or metformin-only group; (c) the trial report provides at least one indicator (endpoint) of the disease status, and (d) participants’ age over 18 years and disease duration at least 1 year before the start of the trial. Exclusion criteria were: (a) RCTs comparing the efficacy and safety of SGLT-2 inhibitor/s against a placebo-controlled group as monotherapy; (b) RCTs comparing SGLT-2 inhibitors with metformin in combination with other antidiabetic drugs in treatment naïve or previously metformin treated patients, (c) the trials comparing SGLT-2 inhibitors–MET as add-on treatment only in one arm, (d) trials provide inadequate information about outcomes of efficacy and safety, and (e) RCTs of less than 12 week duration.

2.3. Quality assessment of the trials

The quality of the RCTs was assessed with Jadad scale [33] which evaluates research articles mentioning trial results from the perspectives of randomization, concealment, and trial success (participant dropout/withdrawal) and their descriptions. At least 3 out of 5 score was decided, a priori, for the RCT report to be included in this systematic review and meta-analysis. Additionally, Critical Appraisal Skills Programme (CASP) guidelines were also followed. The consideration of all randomized participants in the final analysis by a constituent study was adopted only when at least 75% of the participants completed the follow-up.

2.4. Data extraction, synthesis and statistical analysis

The data were extracted by adapting a standardized procedure on pre-determined format from the published research papers.
and other sources of result dissemination. The participants’ demographic, clinical, and pathological characteristics, interventions of the trial, endpoints, and findings were obtained from the research reports dissemination records independently by two researchers. From the RCTs which utilized multiple doses, the higher dose was selected keeping in view the efficacy and tolerability profile. Data were taken preferably from tabular and textual sources, but when necessary, graphic sources were also utilized for data extraction. In order to bring data in input form for the meta-analysis, and to ensure uniformity of units, appropriate calculators were used. Data and Analyses module of Review Manager software (RevMan Version 5.2; Choccrane Collaboration) was used for the meta-analyses based on mean differences between the groups being compared. Means and standard deviation (mean ± standard deviation (SD)) of the changes in variables from baseline were calculated and converted into mean differences along with 95% confidence intervals (95% CI) for each constituent study. The overall effect of treatment was calculated as weighted average of the inverse variance adjusted individual effects (mean differences). To accommodate for between study heterogeneity, the random effect model was chosen. Sensitivity analyses were performed and between study heterogeneity was tested by I² index. Funnel plots were examined for the assessment of publication bias.

3. Results

Seven studies [18–25] met both inclusion and exclusion criteria and were therefore included in the meta-analysis (Fig. 1). The characteristics of these studies are presented in Table 1. Participants in these trials were the T2DM patients having inadequate control of disease by diet/exercise and metformin therapy. Overall, this meta-analysis included 2847 T2DM patients with inadequate control with lifestyle interventions and metformin despite a daily dose range of 1.5–3 g. The proportion of males was 54%. Among the important demographic and clinical features presented as mean ± SD, age of the participants was 55.8 ± 8.4, disease duration since diagnosis was 5.0 ± 4.6 years, HbA1c 7.97 ± 0.85%, FPG 9.36 ± 2.4 mmol/L and BMI 31.7 ± 4.9.

Of the included studies, trial duration was 2 years (two trials), 1 year (one trial), 6 months (two trials), and 3 months (two trials). The SGLT-2 inhibitors studied were dapagliflozin (three trials), canagliflozin (two trials), empagliflozin (one trial), and ipragliflozin (one trial). The majority of these trials fixed HbA1c as the primary outcome measure (five trials) but one trial used change in body weight [19] and one used safety and tolerability as the primary outcome measure [20]. Dosage groups selected from included studies for the meta-analysis are: DAPA 10 mg/day (three trials), CANA 300 mg/day (two trials), EMPA 25 mg/day (one trial), and IPRA 300 mg/day (one trial).

An assessment of the quality of the included RCTs according to Jadad scale was generally good. Bailey et al. [18], Bolinder et al. [19], and Henry et al. [21], which scored 5/5 on this scale, utilized stratified randomization procedures with computer generated codes concealed securely. The treatment allocation was performed by using an interactive online response system in pre-determined balanced groups. The reports of Ferrannini et al. [20] and Lavalle-González et al. [22] scored 4/5 while Rosenstock et al. [24] and Wilding et al. [25] scored 3/5 on Jadad scale. A low-level publication bias was evident from the visual examination of the funnel plots (Fig. 2).

The major findings of the meta-analyses are given in Table 2. In comparison with placebo-MET controls, the SGLT-2 inhibitor–MET therapy resulted in an HbA1c decline with mean difference and 95% CI of −0.47 [−0.66, −0.27]%; P < 0.00001 at 12–24 weeks, −0.37 [−0.77, 0.03]%; P = 0.07 at 1-year and −0.41 [−1.09, 0.28]%; P = 0.24 after 2 years (Fig. 3a–c).

![Flowchart of study screening and selection.](image-url)
Table 1 – Characteristics of the studies included in the meta-analyses.

<table>
<thead>
<tr>
<th>Study/drug/duration</th>
<th>Participants</th>
<th>Participant’s characteristics</th>
<th>Clinical indicators</th>
<th>Metformin dosage (g)</th>
<th>Outcome measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al. (2010, 2013)/DAPA/2 years</td>
<td>Patients: 546 (137 DAPA 2.5 mg, 137 DAPA 5 mg, 135 DAPA 10 mg, and 137 placebo) Administration: once-daily orally before morning meal</td>
<td>Age: 54 ± 9.3</td>
<td>HbA1c (%): 8 ± 0.9</td>
<td>Mean ± SD: 1.8 ± 0.4 g</td>
<td>Primary: HbA1c</td>
<td>Significant and sustained reductions in HbA1c, FPG and BW</td>
</tr>
<tr>
<td>Bolinder et al. (2012) and Ljunggren et al. (2012)/DAPA/1 year</td>
<td>Patients: 180 (89 DAPA and 91 placebo groups) Administration: once daily before or with morning meal as add-on to open-label metformin</td>
<td>Age: 60.7 ± 7.55</td>
<td>HbA1c (%): 7.2 ± 0.5</td>
<td>Mean ± SD: 1.9 ± 0.4</td>
<td>Primary: body weight (BW)</td>
<td>Significant reduction in BW, WC, HbA1c and FPG levels after treatment</td>
</tr>
<tr>
<td>Ferrannini et al. (2012)/EMPA/2 years</td>
<td>Patients: 388 (166 EMPA 10 mg, 166 EMPA 25 mg, and 56 sitagliptin, and 30 placebo) Administration: once-daily with evening meal</td>
<td>Age: 56.2 ± 9.2</td>
<td>HbA1c (%): 7.9 ± 0.8</td>
<td>≥1.5 g/day</td>
<td>Primary: safety and tolerability</td>
<td>EMPA 25 mg was superior to SITA in reducing HbA1c, FPG BW and BP</td>
</tr>
<tr>
<td>Henry et al. (2012)/DAPA/24 weeks</td>
<td>Patients: 598 (397 DAPA and 201 placebo groups) Administration: once daily with evening meal</td>
<td>Age: 52 ± 10</td>
<td>HbA1c (%): 9.2 ± 1.3</td>
<td>Median: 2 g</td>
<td>Primary: HbA1c</td>
<td>Significant reduction in BW, WC, HbA1c and FPG levels</td>
</tr>
<tr>
<td>Lavalle-González et al. (2013)/CANA/26 weeks</td>
<td>Patients: 1264 (736 CANA, 366 sitagliptin, and 183 placebo) Administration: once daily with evening meal</td>
<td>Age: 55.4 ± 9.4</td>
<td>HbA1c (%): 7.9 ± 0.9</td>
<td>≥2 g/day</td>
<td>Primary: HbA1c</td>
<td>Significant reductions in HbA1c, FPG and BW</td>
</tr>
<tr>
<td>Rosenstock et al. (2012)/CANA/12 weeks</td>
<td>Patients: 451 (64 each for CANA 50 mg, 100 mg, 150 mg, and 300 mg BID groups and 18 each for CANA 200 mg, SITA and placebo) (once daily)</td>
<td>Age: 52.9 ± 8.1</td>
<td>HbA1c (%): 7.75 ± 0.9</td>
<td>Mean ± SD: 1.9 ± 0.48 g</td>
<td>Primary: HbA1c</td>
<td>Significant reductions in HbA1c, FPG and BW</td>
</tr>
<tr>
<td>Wilding et al. (2013)/IPRA/12 weeks</td>
<td>Patients: 342 (IPRA 12.5 mg 66, 50 mg 69, 150 mg 67, 300 mg 67 and placebo 66) (once daily)</td>
<td>Age: 57.4 ± 8.4</td>
<td>HbA1c (%): 7.76 ± 0.68</td>
<td>Range: 1.5–3 g/day; 61% patients had 2–3 g daily</td>
<td>Primary: HbA1c</td>
<td>Significant dose dependent decrease in HbA1c, FPG and BW</td>
</tr>
</tbody>
</table>
Between study heterogeneity as estimated by $I^2$ was over 80% in all three durations. Sensitivity analysis, by excluding Ferrannini et al. [20], significantly changed the results of the 1 year (−0.57 [−0.94, −0.19]; $P < 0.004$) and 2 years (−0.80 [−1.35, −0.25]%; $P < 0.004$) comparisons.

The effect size of the FPG decline from baseline when measured as the mean difference between SGLT-2 inhibitor–MET and placebo-MET groups along with 95% CI was −1.16 [−1.56, −0.75] mM/L; $P < 0.00001$ in 12–24 weeks, −0.34 [−0.77, 0.09] mM/L; $P < 0.0001$ in 1 year and −0.55 [−0.99, −0.11] mM/L; $P < 0.02$ in 2 years. Over 50% heterogeneity was observed only in the 12–24 week comparison.

The SGLT-2 inhibitor–MET combination reduced body weight significantly compared to placebo-MET combination.
in the comparisons of all three durations (Table 2 and Fig. 3b). Least between-study heterogeneity was observed for the body weight comparisons.

Whereas, the SGLT-2 inhibition combined with metformin also resulted in a decline in systolic blood pressure from baseline in 12–24 week duration studies with a mean difference 95% CI of $-3.45$ [−5.11, −1.79] mmHg; $P < 0.0001$, this difference was not maintained in the 2 year trial (−1.80 [−6.18, 2.58] mmHg; $P = 0.42$). Similarly, the SGLT-2 in inhibition led to diastolic blood pressure changes at 12–24 weeks of $-0.86$ mmHg; $P < 0.0005$ and in the 2 year trial of $-0.86$ mmHg; $P = 0.89$. Heterogeneity was 0% in the 12–24 week duration comparisons in both these parameters.

Only one study needed rescue therapy for a significantly high number of participants (60% in the placebo–MET and 42% in DAPA 10 mg/day groups [18]). In the rest of the studies less than 20% of participants required rescue therapy in any group.

The safety profile of the SGLT-2 inhibitor–MET combination synthesized as an average effect of the included studies was generally similar in both treated and control groups (Table 3). The prevalence of ‘at least one study-related AE’ was 13% in the control group and 18% in the treated group. The prevalence of events suggestive of genital infections was 2% in the control group and 7% in the treated group.

### Table 2 – Major findings of the meta-analysis.

<table>
<thead>
<tr>
<th>Parameter/duration</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Change from baseline (mean ± SD)</th>
<th>Mean difference [95% CI]</th>
<th>Significance level (P)</th>
<th>Heterogeneity (I²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td>SGLT-2 Inh</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12–24 weeks</td>
<td>7</td>
<td>1543</td>
<td>−0.9 ± 0.77</td>
<td>−0.5 ± 0.74</td>
<td>−0.47 [−0.66, −0.27]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>After 1 year</td>
<td>3</td>
<td>527</td>
<td>−0.7 ± 0.86</td>
<td>−0.3 ± 0.75</td>
<td>−0.37 [−0.77, 0.03]</td>
<td>0.07</td>
</tr>
<tr>
<td>After 2 years</td>
<td>2</td>
<td>280</td>
<td>−0.8 ± 1.03</td>
<td>−0.3 ± 1.02</td>
<td>−0.41 [−1.09, 0.28]</td>
<td>0.24</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12–24 weeks</td>
<td>7</td>
<td>1581</td>
<td>−1.7 ± 1.7</td>
<td>−0.5 ± 1.66</td>
<td>−1.16 [−1.56, −0.75]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>After 1 year</td>
<td>1</td>
<td>195</td>
<td>−2 ± 1.78</td>
<td>−1.66 ± 1.19</td>
<td>−0.34 [−0.77, 0.09]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After 2 years</td>
<td>2</td>
<td>467</td>
<td>−1.6 ± 1.76</td>
<td>−1 ± 1.67</td>
<td>−0.55 [−0.99, −0.11]</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12–24 weeks</td>
<td>7</td>
<td>1571</td>
<td>−3.1 ± 3.44</td>
<td>−0.7 ± 2.78</td>
<td>−2.28 [−2.67, −1.88]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>After 1 year</td>
<td>3</td>
<td>659</td>
<td>−3.6 ± 4.22</td>
<td>−1.1 ± 3.39</td>
<td>−2.60 [−3.17, −2.03]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>After 2 years</td>
<td>2</td>
<td>465</td>
<td>−2.8 ± 5.17</td>
<td>0.24 ± 4.32</td>
<td>−3.03 [−3.90, −2.16]</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12–24 weeks</td>
<td>4</td>
<td>867</td>
<td>−4.5 ± 8.8</td>
<td>−0.1 ± 7.6</td>
<td>−3.45 [−5.11, −1.79]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After 2 years</td>
<td>2</td>
<td>166</td>
<td>−0.3 ± 13.7</td>
<td>1.5 ± 15</td>
<td>−1.80 [−6.18, 2.58]</td>
<td>0.42</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12–24 weeks</td>
<td>4</td>
<td>845</td>
<td>−2.26 ± 7.92</td>
<td>−0.6 ± 8.11</td>
<td>−1.91 [−2.96, −0.86]</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>After 2 years</td>
<td>2</td>
<td>166</td>
<td>−1.2 ± 10.1</td>
<td>−1 ± 7.9</td>
<td>−0.20 [−2.94, 2.54]</td>
<td>0.89</td>
</tr>
</tbody>
</table>

### Table 3 – Prevalence (%) of adverse reactions in the included studies.

<table>
<thead>
<tr>
<th>Adverse events (AE)</th>
<th>C</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one AE</td>
<td>52 ± 18</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>At least one related AE</td>
<td>13 ± 6</td>
<td>19 ± 8</td>
</tr>
<tr>
<td>At least one serious AE</td>
<td>3 ± 4</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>4 ± 2</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 ± 3</td>
<td>4.5 ± 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 ± 3</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 ± 2</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>Genital infections</td>
<td>0.5 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Suspected genital infections</td>
<td>2 ± 2</td>
<td>8 ± 7</td>
</tr>
<tr>
<td>Headache</td>
<td>3 ± 2</td>
<td>5.5 ± 6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 ± 6</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>7 ± 4</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>3 ± 2</td>
<td>3.5 ± 2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 ± 1</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Renal dysfunction/failure</td>
<td>2 ± 1</td>
<td>2 ± 2</td>
</tr>
</tbody>
</table>

4. Discussion

This systematic review examined the effectiveness of SGLT-2 inhibiting drugs as add-on treatment to metformin in people with inadequate controlled T2DM on metformin alone. There was a significant effect of the SGLT-2 inhibitor–MET combination in improving HbA1c, FPG, body weight, and blood pressure during the first 6-month treatment, but afterwards, the efficacy of this combinational therapy was not consistent in the included studies. In the long term (1 year and 2 year duration trials), the SGLT-2 inhibitor–MET was not found to significantly differ from placebo-MET in reducing HbA1c. However, sensitivity analysis resulted in attainment of significant effects of SGLT-2 inhibitors–MET in reducing HbA1c in the comparisons of all three durations. The FPG was significantly reduced by the SGLT-2 inhibitor–MET combination therapy in all three comparisons. Body weight reductions were also highly significant in the SGLT-2 inhibitor–MET groups.

When compared as monotherapies, SGLT-2 inhibitors were not found to be superior to metformin in reducing HbA1c and FPG in RCTs with T2DM patients after 12 weeks [34] and 2 years [30]. However, SGLT inhibition reduced body weight more than metformin in both of these trials. A more recent report of a placebo-controlled RCT revealed that SGLT-2 inhibition with DAPA in addition to ongoing antihyperglycemic therapies in T2DM patients with moderate renal impairment (duration of
Fig. 3 – Efficacy of the SGLT-2 inhibitors in combination with metformin in reducing percent HbA1c in different durations: (a) 12–24 weeks, (b) 1 year, and (c) 2 years in T2DM patients.

disease $17 \pm 9.5$) could not provide better glycemic control. However, it was able to reduce FPG, blood pressure, and body weight.

There are also some reports of RCTs that compared SGLT-2 inhibitor–MET with other contemporary drugs. Nauck et al. [26] compared DAPA–MET with glipizide–MET and found that DAPA–MET combination reduced body weight significantly more than comparators after 1 year but differences were not pronounced in reducing Hba1c and FPG. On the other hand, three trials which compared SGLT-2 inhibitor–MET with a comparator found superiority of the former combination over comparators in reducing Hba1c, FPG, body weight, and blood pressure [20,22,29].

The superiority of the SGLT-2 inhibitor–MET combination against the comparators [20,22,29] in reducing Hba1c on the one hand, and the non-significant difference against placebo–MET or metformin only groups [30,34] and as has been seen in this meta-analysis of 1 year and 2 year durations, suggests that more trial data may be required to fully assess this combination. However, the combination of metformin and SGLT-2 inhibitors has other patient benefit including reducing body weight [34]. Furthermore, the SGLT-2 inhibitors which act independently of insulin status, pose a low hypoglycemia risk. Thus, these anti-diabetic drugs in combination with metformin can be a valuable therapeutic regimen in the armamentarium against T2DM.

Because of its kidney-based mechanism of action, concerns about the SGLT-2 inhibitors’ possible effects on the renal tubular transportation of bone minerals are also being considered. In an international, randomized, double-blind, placebo-controlled trial, which enrolled patients with inadequate control on T2DM with metformin has demonstrated that a 50-week dapagliflozin treatment did not result in any significant changes in markers of bone formation and resorption [23]. The SGLT-2 inhibition has not been found to adversely affect renal function or electrolyte composition of clinical significance [35] rather the diuretic effect of SGLT-2 inhibitors improves blood pressure in hypertension patients. Moreover, SGLT-2 inhibitors are tolerated well by chronic kidney patients in a 26-week RCT [36]. Although this meta-analysis found non-significant differences in the safety profile between the SGLT-2 inhibitor–MET and placebo-MET groups, there are reports of increased confirmed and suspected urinary tract infections and genital tract problems [21,35]. SGLT-2 inhibition is associated with a slightly higher incidence of urinary/genital tract infections [37]
which is generally attributed to higher urinary glucose levels responsible for providing substrate to microorganisms especially fungal growth [28]. In the present study, synthesis of adverse events data from included studies indicated a higher incidence of events suggestive of genital infections. Counseling patients about genital hygiene can minimize the risk of infection.

In this meta-analysis, heterogeneity was above 80% in the comparisons of HbA1c change of all three durations (Table 2) while in the rest it was either absent or low. Generally, it is considered that clinical and methodological heterogeneity dictates statistical heterogeneity. Furthermore, the trials were not only multi-center, but also multi-national and even multi-continental and each center contributed a relatively small number of patients, which might have led to a high degree of variability in the overall measures of central tendency. Funnel plot asymmetry is generally ascribed to publication bias which is not pronounced in the present study.

In the included studies, missing data were less than 20%, except for one study [18] in which 60% placebo-MET treated patients required rescue therapy and the number decreased in a dose-dependent manner from 52% in 2.5 mg/day, 46% in 5 mg/day to 42% DAPA 10 mg/day treated groups. In this meta-analysis, data of the participants have been utilized who actually completed the trial duration, however. Completion rates for placebo-controlled trials were 69–96% for placebo groups and 81–100% for SGLT-2 inhibitor groups with rescue rates ranging from 7 to 60% for placebo groups and 0 to 42% for SGLT-2 inhibitor groups. Nevertheless, better ways are needed to analyze datasets with significant missing data in order to improve evidence quality [38].

The important limitations of the present study include all possible data were not available by the time of finalization of this research; between-study statistical heterogeneity was high at least in some comparisons; for 1 year and 2 year duration, the number of studies was smaller; and although the majority of the studies recruited patients with ongoing metformin, one study [21] recruited patients who were treatment naive.

5. Conclusion

The SGLT-2 inhibition based pharmacotherapies for T2DM patients are currently in a development phase and one important aspect of diabetes management is to explore co-administration of SGLT-2 inhibitors with metformin which is the first line drug to control this disease. This meta-analysis, which compared SGLT-2 inhibitor–MET combination with placebo–MET control reveals that SGLT-2 inhibition in combination with metformin is a potential therapeutic option based on its effects on glycemic control, body weight, blood pressure but this area needs further research to clarify the efficacious characteristics of this bitherapy in glycemic control. A few long-term trials can help in arriving conclusive evidence required to judge the potentials of this therapeutic intervention.

Conflict of interest

The authors declare that they have no conflict of interest.

References


