Efficacy and Safety of Empagliflozin in Type 1 Diabetes Mellitus Patients: A Systematic Review

Empagliflozinin Tip 1 Diabetes Mellitus Hastalarında Etkililiği ve Güvenliliği: Sistematik Bir Derleme

 Sumanta SAHA, Sujata SAHA*

R. G. Kar Medical College, Kolkata, West Bengal, INDIA
*Mankar College, West Bengal, INDIA

Abstract

As the efficacy and safety of empagliflozin remain poorly studied in Type 1 diabetes mellitus (T1DM) patients, this narrative-systematic review aims to review it. The randomized controlled trials studying the above across different empagliflozin dosages and placebo got searched in PubMed, Embase, and Scopus databases. The database searches yielded 5 eligible trials reporting data of about 1,870 T1DM patients from 45 countries. The empagliflozin dosages tested in these trials were 2.5, 10, and 25 mg. The trials collectively showed a low or unclear risk of bias (Cochrane tool used). The existing double-blinded randomized controlled trials mainly suggest a dose-dependent decrease in glycated hemoglobin, body weight, and total weekly insulin requirement in empagliflozin-treated T1DM patients. Ketoacidosis, urinary tract infection, and study discontinuation due to side effects were rare adverse effects of empagliflozin. Genital infection predominantly occurred among recipients of 10 or 25 mg empagliflozin.

Keywords: Empagliflozin;
sodium-glucose transporter 2 inhibitors;
Type 1 diabetes mellitus; treatment outcome;
adverse effects

Özet

Tip 1 diabetes mellitus (T1DM) hastalarında, empagliflozinin etkililiği ve güvenliliği hâlen yeterince çalışılmamış olduğundan bu geleneksel-sistematik derlemede, bu konunun gözden geçirilmesi amaçlandı. Farklı empagliflozin dozajları ve plasebo alan hastalarda, yukarıdaki kriterleri analiz eden randomize kontrollü çalışmalar için PubMed, Embase ve Scopus veri tabanları tarandı. Tarama sonrası 45 ülkeden yaklaşık 1.870 T1DM hastasının verilerini rapor eden 5 uygun çalışma seçildi. Bu çalışmalarda test edilen empagliflozin dozajları 2,5, 10 ve 25 mg idi. Çalışmalardaki ön yargı riski, genel olarak düşük veya belirsizdi (Cochrane aracı kullanıldı). Mevcut çift-kör, randomize kontrollü çalışmalar, empagliflozin ile tedavi edilen T1DM hastalarında glikolize hemoglobin, vücut ağırlığı ve haftalık toplam insülin gereksiniminde doza bağlı bir azalma olduğunu ortaya koydu. Ketoasidoz, idrar yolu enfeksiyonu ve yan etkiler nedeniyle çalışmanın kesilmesi, empagliflozinin nadir görülen yan etkileriydi. Genital enfeksiyon ise ağırlıklı olarak 10 veya 25 mg empagliflozin alanlarda meydana geldi.

Anahtar kelimeler: Empagliflozin;
sodyum-glukoz transporter 2 inhibitörleri;
Tip 1 diabetes mellitus; tedavi sonucu;
yan etkiler

Introduction

Type 1 diabetes mellitus (T1DM) is primarily a childhood-onset hyperglycemic autoimmune condition resulting from the death of pancreatic beta cells. It's triggered by genetic predisposition (human leukocyte antigen alleles such as DQ and DR) or viruses or environmental toxins, and other unknown factors (1,2). These patients are at risk of hyperglycemic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic ketoacidosis, and

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diabetic foot (1,2). Due to the lack of production of the anabolic hormone insulin, these patients require lifelong insulin treatment. However, the latter has drawbacks. First, it fails to achieve the desired glycemic control in most T1DM patients. Nearly 75% of these patients do not obtain the desired glycemic control [glycated hemoglobin (HbA1c) of <7%, as recommended by the American Diabetes Association] (3,4). Second, the sole dependence on insulin as the only glucose-lowering agent increases hypoglycemia and long-term cardiovascular risk-related mortality (5). Besides, there is also concern regarding the quality of life of T1DM patients due to the intricacies and difficulties associated with multiple daily insulin injections and finger pricks for the self-monitoring of blood glucose levels (6). Therefore, empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), has attracted substantial attention as a plausible independent or insulin-adjunct drug to control hyperglycemia in T1DM patients. SGLT2i drugs flush out glucose from the body by blocking the SGLT2 transport protein in the proximal renal tubules (7,8). In healthy individuals, these proteins absorb almost 90% of the glucose filtered through the renal tubules (7,8). The chemical conformation of empagliflozin is $C_{23}H_{27}ClO_7$ (9). These molecules weigh about 450.91 g/mol (9). Due to its extended half-life of about 10 to 12 h and consequent feasibility of one dose per day, empagliflozin has drawn substantial attention among the SGLT2i drugs (6,9). Besides, as the drug undergoes glucuronidation, no key metabolites are produced (6,9). Empagliflozin has proven to be beneficial in achieving glycemic control in T2DM patients on diet and exercise treatment (10), and the U.S. Food and Drug Administration (FDA) recommends its use in these patients (9,11). It also decreases the cardiovascular risk in T2DM patients (10). The major adverse events reported among T2DM patients include a drop in blood pressure and blood glucose (when simultaneously administered with insulin) levels, ketoacidosis, impairment of kidney function, fungal infection of the genitals, and raised levels of low-density lipoproteins (LDL) (10,11). Besides, in T2DM patients, the urinary glucose excretion threshold has a dose-dependent relationship with empagliflozin dosages; it rises by 11 and 18-fold with a dosage of 10 and 25 mg empagliflozin, respectively (9). Unlike T2DM patients, the efficacy and safety of empagliflozin remain poorly established in T1DM patients. Presently, the FDA does not approve the use of empagliflozin in T1DM patients (2,12). The effects of empagliflozin at dosages of 2.5, 10, and 25 mg on T1DM patients have been tested in several studies (13-17). However, to our best knowledge, there is no exclusive review article on the efficacy and safety of empagliflozin in T1DM patients. The existing review of literature is mainly concentrated on the holistic application of SGLT2i drugs (2,3,6,18-30) or limited to a specific outcome (31). Therefore, this review aims to study the variation in the efficacy and safety of empagliflozin across its dosages in T1DM patients.

Material and Methods

This review used a pre-registered (PROSPERO: registration no. CRD42019135844) (32) and pre-published protocol (33). Its reporting followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA statement, 2009) (34).

Inclusion Criteria

1. Study population: T1DM patients aged ≥18 undergoing active insulin treatment, irrespective of their duration of diabetes. The T1DM diagnosis and the route of administration, dosage, and regimen of insulin therapy were accepted according to the trialists.
2. Study design: Double-blinded randomized controlled (parallel arm) trials, irrespective of trial duration and number of treatment arms, were eligible.
3. Intervention arms: The participants in the intervention arm received 25 mg empagliflozin once daily.
4. Comparator arm: The comparator arms received either empagliflozin at a dose of <25 mg once daily and/or a placebo.
5. Outcomes: The primary efficacy outcomes of interest were HbA1c level (%), fasting plasma glucose (FPG) levels (mmol/L), and urine glucose excreted over 24 h (gm/24 h). The secondary outcomes of interest included the weekly requirement of total insulin dosage (U/kg), systolic blood

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pressure (SBP) and diastolic blood pressure (DBP) (mmHg), body weight (kg), and blood lipid parameters (mmol/L) such as LDL and high-density lipoprotein, total cholesterol, and triglycerides. The primary safety outcomes of interest included ketoacidosis, urinary tract infection (UTI), Fournier's gangrene, amputation of limb/s, kidney function impairment, bone fracture, infection of genitals, and adverse effects related to volume depletion. The secondary safety outcome of interest was the discontinuation of the participants from the study due to side effects. For ketoacidosis, only the established cases received consideration.

Exclusion Criteria

1. Study design other than that described above, such as observational studies.
2. Study participants diagnosed with any other type of diabetes, such as T2DM or gestational DM.
3. T1DM patients treated with any hypoglycemic agent besides insulin and empagliflozin.
4. Animal studies.

If more than one article sourced data from the same study population, as indicated by matching the trial registration numbers, the trial that reported the larger number of outcomes was incorporated.

Database Search

A search of titles and abstracts of trials fulfilling the above criteria was performed in PubMed, Scopus, and Embase, irrespective of their geographical origin, publication date, and language. The last database search was performed on 06-Mar-2021. The database search strategy used for the PubMed search is depicted in a supplementary table (Appendix 1). Besides, the bibliography of the articles read in full-text was scrutinized for any additional citations. Citations retrieved by the search of the databases were uploaded in a systematic reviews software "Rayyan" (35). Then, the duplicate articles were eliminated, after which, the titles and abstracts of these citations were skimmed. Articles that appeared eligible or potentially suitable for inclusion based on their abstract were read completely. The excluded papers were listed, and reasons for their exclusion are provided.

Data Abstraction and Risk of Bias Assessment

The study design, population characteristics, interventions received by participants in different treatment arms, and the reported outcomes of interest from articles included in this review were summarized in a pre-piloted form for data abstraction. Subsequently, the risk of bias was assessed using the Cochrane tool (36). The random number generation method and concealing technique of the interventions allocated to the different treatment arms were used to assess the risk of selection bias. The performance bias was determined by studying the method used to blind the study personnel and participants of the interventions allocated to the different treatment arms. By evaluating the blinding method used for assessors of the outcome, the risk of detection bias was assessed. Moreover, by studying the balance and causes of missing outcome data between the different intervention arms, the risk of attrition bias was assessed. The evaluation of reporting bias contrasted the reported results with the pre-stated notions of the trialists. Any other risk of bias that did not fit into the above types was categorized as other risks of bias. Each component of the risk of bias was categorized as low, high, and unclear based on the observed extent of bias.

Authors' role

The authors of this review independently conducted the database search, study selection, data abstraction, and assessment of the risk of bias. The authors resolved all conflicts in opinions through discussion and mutual consent and did not require any third-party insight or contact with the trialists.

Synthesis of results

Due to few available trials (<10), a narrative review was conducted. For efficacy-related outcomes, the mean changes from the baseline caused by the corresponding empagliflozin dosages were evaluated compared to placebo. The frequencies of the safety outcomes were checked across different intervention arms. At the end of the trial period, the outcomes were evaluated. Assessments of publication bias and statistical

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Appendix 1. Search strategy (PubMed) (search date: 06-Mar-2021).		
Search ID No.	Search terms	No. of search results
1	"sodium-glucose cotransport*"[Title/Abstract] OR "sodium glucose cotransport*"[Title/Abstract] OR "Sodium-Glucose Transporter 2 Inhibitors" [Title/Abstract] OR SGLT*[Title/Abstract] OR "SGLT2-inhibitors"[Title/Abstract] OR "SGLT2 inhibitors"[Title/Abstract] Empagliflozin[Title/Abstract] OR Jardiance[Title/Abstract]	1,069
2	"insulin-dependent diabetes mellitus"[Title/Abstract] OR "type 1"[Title/Abstract] OR type-1[Title/Abstract] OR "juvenile-onset diabetes"[Title/Abstract]	194,213
3	efficacy[Title/Abstract] OR benefit*[Title/Abstract] OR effective*[Title/Abstract] OR safety[Title/Abstract] OR "adverse event"[Title/Abstract] OR "side effect"[Title/Abstract] OR tolerance[Title/Abstract]	36,91,256
4	"Diabetes Mellitus, Type 1"[Mesh]	77,593
5	"diabetes mellitus, type 1/drug therapy"[MeSH Terms]	14,687
6	("Glucosides/adverse effects"[Mesh] OR "Glucosides/toxicity"[Mesh])	4,426
7	"sodium glucose transporter 2 inhibitors/administration and dosage"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors/adverse effects"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors/toxicity"[MeSH Terms]	519
8	("Benzhydryl Compounds/administration and dosage"[Mesh] OR "Benzhydryl Compounds/adverse effects"[Mesh] OR "Benzhydryl Compounds/therapy"[Mesh] OR "Benzhydryl Compounds/toxicity"[Mesh])	5,420
Search IDs combined	1+2+3	3
	1+2	5
	4 OR 5 AND 6 OR 1	95
	7 AND 4	35
	8+4	31
	Total PubMed search results	169

heterogeneity were not possible due to the non-quantitative nature of this review.

Results

Scope of The Review

The database search yielded 527 publications. After eliminating duplicates and skimming through the titles and abstracts of 428 articles, 9 articles were selected for full-text reading. Of these 9 articles, 5 were excluded, and the remaining (37-40) were included in this review (Figure 1). The reasons for the exclusion of the full-text read articles were studies based on the same trial population that was already included in this review, the study population was unclear or consisted of T2DM patients, and the lack of a control arm.

Four eligible trials were included in this review (37-40). These studies sourced data from 1,870 T1DM patients of 45 countries. Two of these trials [empagliflozin as an adjunct to insulin therapy (EASE) 2 and 3] were reported in one research article (37). The follow-up duration ranged from 14 to 364 days, with an average of about 134.4 days (37-40). The estimated glomerular filtration rate (eGFR) among the trial participants was >60 mL/min/1.73 m^2 (38-40). In one trial, <4% of the patients had an eGFR of <60 mL/min/1.73 m^2 (37). The pre-trial HbA1c among the trial participants was about 7-10% (37-40). The EASE 1, 2, and 3 trials were conducted in 2 (Austria and Germany), 17, and 24 countries, respectively. The trial by Shimada et al. (39) and Lunder et al. (40) was conducted in Japan and Ljubljana, respectively. The average age of the trial participants was about 39-46 years (37-40). The risk of
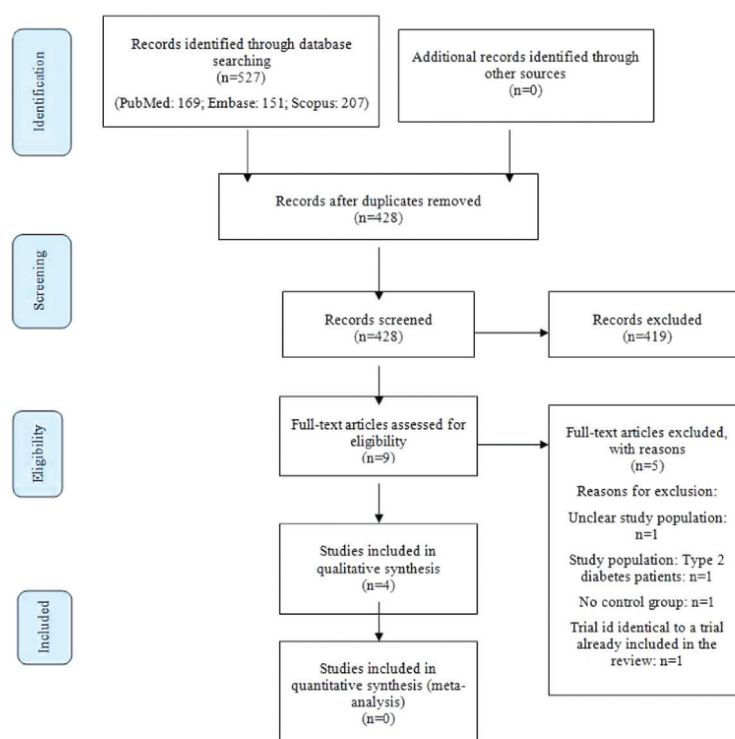
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Figure 1. PRISMA diagram [From: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097. doi:10.1371/journal.pmed1000097].

performance and detection bias were unclear. The remaining bias components generally carried a low risk of bias. The salient features of the trials and the assessment of their risk of bias are presented in Table 1 and Table 2, respectively.

The trials EASE 1 and 3, and that by Shimada et al. tested 2.5, 10, and 25 mg dosages (37-39). The EASE 2 trial tested the 10 and 25 mg dosages (37). The trial by Lunder et al. tested 25 mg empagliflozin alone, metformin alone, empagliflozin with metformin, and placebo, and reported the following efficacy outcomes of interest - HbA1c, SBP, and DBP (40). For each intervention arm, the mean baseline values of the efficacy outcomes, their mean changes from the baseline by the end of the trial period, and the comparison of these changes between arms receiving different dosages of empagliflozin and the placebo arm are presented in Table 3. The frequencies of the occurrence of the corresponding safety outcomes are presented in Table 4.

Efficacy Outcomes

HbA1c

By the end of the trial period of the EASE 1 and 3 trials and that of Shimada et al., a dose-dependent decrease in the mean HbA1c from the baseline was observed in the 2.5, 10, and 25 mg dosages of empagliflozin, and these changes were statistically different from the placebo (37-39). Moreover, in the EASE 2 trial, patients receiving 25 mg of empagliflozin showed a greater drop in the HbA1c levels than those receiving 10 mg, and these differences were statistically significant compared to patients receiving placebo (37). In the trial by Lunder et al., only the group receiving a combination of empagliflozin and metformin showed a statistically significant change in the HbA1c levels (0.6%) (40).

Fasting Plasma Glucose

In both EASE 2 and 3 trials, a dose-dependent decrease in the FPG levels was observed from baseline, which was statistically significant compared to the placebo (37).

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Table 1. Salient features of the reviewed trials.

Trial name/study author, year	Study design and characteristics	Population characteristics	Intervention arms	Outcomes of interest reported
EASE 1 (38)	Trial description: Randomized, double-blind, phase 2 trial Multicentric Trial country: Germany and Austria Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT01969747	Number of participants: n=75 Empagliflozin 2.5 mg arm: mean (SD) age: 41.9 (9.7) years Empagliflozin 10 mg arm: mean (SD) age: 39.6 (11.6) years Empagliflozin 25 mg arm: mean (SD) age: 41.9 (9.7) years Placebo arm: mean (SD) age: 40.5 (10.6) years	Empagliflozin 25 mg arm: n=18 Empagliflozin 10 mg arm: n=19 Empagliflozin 2.5 mg arm: n=19 Placebo arm: n=19 Intervention duration: 4 weeks	HbA1c, FPG, UGE, total insulin requirement, body weight, SBP, DBP, total cholesterol, LDL, HDL, triglycerides
EASE 2 (37)	Trial description: Randomized, double-blinded trial Multicentric Ethical clearance: Obtained Consent: obtained Funding information: provided Clinical trial registration: NCT02414958	Number of participants: n=723 Empagliflozin 10 mg arm: mean (SD) age: 45.7 (12.5) years Empagliflozin 25 mg arm: mean (SD) age: 45.3 (13.9) years Placebo arm: mean (SD) age: 44.5 (13.5) years	Empagliflozin 10 mg: n=243 Empagliflozin 25 mg: n=241 Placebo: n=239 Duration: EASE 2: 52 weeks	HbA1c, FPG, total insulin dose requirement, body weight SBP, DBP, ketoacidosis, UTI, limb amputation, renal impairment, bone fracture, genital infection, volume depletion-related side effects, and study discontinuation due to side effects
EASE 3 (37)	Trial description: Randomized, double-blinded trial Multicentric Ethical clearance: Obtained Consent: obtained Funding information: provided Clinical trial registration: NCT02580591	Number of participants: n=723 Empagliflozin 2.5 mg arm: mean (SD) age: 43.4 (14.2) years Empagliflozin 10 mg arm: mean (SD) age: 42.4 (13.3) years Empagliflozin 25 mg arm: mean (SD) age: 44.2 (13.5) years Placebo arm: mean (SD) age: 42.2 (13.2) years	Empagliflozin 2.5 mg arm: n=237 Empagliflozin 10 mg: n=244 Empagliflozin 25 mg: n=242 Placebo: n=238 Duration EASE 3: 26 weeks	HbA1c, FPG, total insulin dose requirement, body weight SBP, DBP, ketoacidosis, UTI, limb amputation, renal impairment, bone fracture, genital infection, volume depletion-related side effects, and study discontinuation due to side effects
Shimada et al., 2018 (39)	Trial description: Randomized, double-blinded phase 2 trial Multicentric trial Trial country: Japan Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT02702011	Study participants (n)=48 (47 completed the 4 weeks trial) Empagliflozin 2.5 mg arm: mean (SD) age: 44.2 (12.6) years Empagliflozin 10 mg arm: mean (SD) age: 44.5 (11.8) years Empagliflozin 25 mg arm: mean (SD) age: 46.6 (10.8) years Placebo group: mean (SD) age: 43.9 (11.7)	Empagliflozin 25 mg arm: n=12 Empagliflozin 10 mg arm: n=12 Empagliflozin 2.5 mg arm: n=13 Placebo arm: n=11 Intervention duration: 4 weeks	HbA1c, FPG, UGE, total insulin dosage requirement, body weight, SBP, DBP, ketoacidosis, UTI, limb amputation, renal impairment, bone fracture, genital infection, volume depletion-related side effects, and study discontinuation
Lunder et al., 2018 (40)	Trial description: A double-blinded randomized controlled trial Single centered trial Trial country: Slovenia Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT03639545	Number of participants: n=40 Empagliflozin group mean (SE) age: 46.0 (2.3) years Metformin group: mean (SE): 46.4 (3.9) Metformin/empagliflozin group: mean (SE): 43.3 (2.6) Placebo group mean (SE) age: 43.1 (2.1) years	Empagliflozin 25 mg arm: n=10 Empagliflozin 25 mg/metformin 2,000 mg arm: n=10 Metformin 2,000 mg arm: n=10 Placebo arm: n=10 Intervention duration: 12 weeks	HbA1c, SBP, and DBP

EASE: Empagliflozin as an adjunctive to insulin therapy; SD: Standard deviation; SE: Standard error; HbA1c: Glycated hemoglobin; FPG: Fasting plasma glucose; UGE: 24-hour urine glucose excretion; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; UTI: Urinary tract infection.

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Table 2. Assessment of the risk of bias (36).

Trial/study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment					
EASE 1 (38)	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
	Authors' comment: The blinding of participants, personnel, and outcome assessors was unclear						
EASE 2 and 3 (37)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
	Authors' comment: Precise mechanism of random sequence generation and its allocation and blinding of personnel, participants, and outcome assessors were unclear						
Shimada et al., 2018 (39)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
	Authors' comment: Although the trialists mentioned that participants, investigators, and personnel were blinded until trial completion, the precise mechanism of it was unclear						
Lunder et al., 2018 (40)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
	Authors' comment: Precise mechanism of random sequence generation and its allocation and blinding of personnel, participants, and outcome assessors were unclear						

EASE: Empagliflozin as an adjunctive to insulin therapy.

By the end of the EASE 2 trial period, the decrease in the FPG levels was by 16.1 and 12.7 mg/dL in the groups administered 25 and 10 mg empagliflozin, respectively (37). In the EASE 3 trial, the decrease was by 25.6, 18.3, and 13.3 mg/dL in the groups administered 25, 10, and 2.5 mg empagliflozin, respectively (37). In the EASE 1 trial, although a dose-dependent decrease in these levels was observed compared to baseline, it was not statistically significant compared to the placebo (38). In the trial by Shimada et al., this decrease was observed across all doses, although it was statistically significant only in the 25 mg empagliflozin group (difference in mean change in FPG compared to placebo:-59.57 mg; 95% confidence interval:-105.65 to -13.49; p=0.0126) (39).

Glucose Excretion Through Urine in 24 Hours (gm/24 h)

The EASE 1 trial and that by Shimada et al. reported an increase in the 24-hour urine glucose excretion in a dose-dependent manner, and these changes were statistically significant compared to the placebo (39). In participants receiving empagliflozin at dosages of 2.5, 10, and 25 mg, the average level of glucose excreted in the urine in 24 hours increased from 13-21 gm to above 80 gm (38). In the trial by Shimada et al., the baseline excretion across the different doses of empagliflozin increased from 14-21 gm (39) to >100 mg by the end of the trial (39).

Total Weekly Insulin Dose Requirement (U/kg)

A dose-dependent decline in the total weekly insulin requirement compared to baseline was observed in participants of the EASE 1, 2, and 3 trials, as well as in the trial by Shimada et al., by the end of the respective trial periods, and this was statistically significant compared to the placebo (37-39).

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Table 3. Summary of efficacy data for the outcomes of interest.

Outcome	Time of measurement	EASE 1 (38) Placebo	EASE 1 Empagliflozin (2.5 mg)	EASE 1 Empagliflozin (10 mg)	EASE 1 Empagliflozin (25 mg)	EASE 2 (37) Placebo	EASE 2 Empagliflozin (10 mg)	EASE 2 Empagliflozin (25 mg)	EASE 3 (37) Placebo	EASE 3 Empagliflozin (2.5 mg)	EASE 3 Empagliflozin (10 mg)	EASE 3 Empagliflozin (25 mg)	Shimada et al., 2018 (39) Placebo	Shimada Empagliflozin (2.5 mg)	Shimada Empagliflozin (10 mg)	Shimada Empagliflozin (25 mg)	Lunder et al., 2018 (40) Placebo	Lunder Empagliflozin (25 mg daily)	Lunder Metformin (2,000 mg daily)	Lunder Empagliflozin (25 mg daily)/metformin (2,000 mg daily)
Mean HbA1c (%)	Baseline	8.18	8.35	8.28	8.15	8.13	8.10	8.06	8.19	8.14	8.19	8.19	8.23	8.02	8.12	7.89	7.8	7.8	7.9	7.8
	Change by the end of trial period	-0.18	-0.53	-0.54	-0.67	-	-0.39	-0.45	-	-0.28	-0.45	-0.52	-0.21	-0.41	-0.56	-0.41	0.1	0.4	0.2	0.6
	Comparison with placebo	-	-0.35% (95% CI: -0.62, -0.09) p=0.010	-0.36% (95% CI: -0.62, -0.10) p=0.008	-0.49% (95% CI: -0.75, -0.22) p<0.001	-	p<0.0001	p<0.0001	-	p<0.0001	p<0.0001	p<0.0001	-	-0.20 (95% CI: -0.48, 0.08) p=0.1488	-0.35 (95% CI: -0.63, -0.07) p=0.0157	-0.20 (95% CI: -0.49, 0.08) p=0.1620	-	p≥0.05	p≥0.05	p<0.05
Fasting plasma glucose (mean)	Baseline	9.15	10.36 mmol/L	9.85 mmol/L	9.81 mmol/L	179.9	174.4 mg/dL	184.6 mg/dL	177.0	175.9 mg/dL	185.0 mg/dL	184.6 mg/dL	194.00	189.08 mg/dL	187.82 mg/dL	147.75 mg/dL	-	-	-	-
	Change by the end of trial period	1.26	0.01 mmol/L	-0.45 mmol/L	-0.70 mmol/L	15.7	-12.7 mg/dL	-16.1 mg/dL	-3.8	-13.3 mg/dL	-18.3 mg/dL	-25.6 mg/dL	-3.04	-17.31 mg/dL	-46.67 mg/dL	-62.61 mg/dL	-	-	-	-
	Comparison with placebo	-	-1.25 (95% CI: -3.56, 1.07) p=0.286	-1.71 (95% CI: -4.04, 0.63) p=0.149	-1.96 (95% CI: -4.32, 0.40) p=0.103	-	-28.4 (95% CI: -41.6, -15.2) p<0.0001	-31.8 (95% CI: -44.7, -18.8) p<0.0001	-	-9.5 (95% CI: -21.7, 2.7) p=0.1278	-14.5 (95% CI: -26.8, -2.3) p=0.0201	-21.8 (95% CI: -34.0, -9.7) p=0.0004	-	-14.27 (95% CI: -58.73, 30.18) p=0.5201	-43.63 (95% CI: -89.72, 2.46) p=0.0629	-59.57 (95% CI: -105.65, -13.49) p=0.0126	-	-	-	-
24-hour urine glucose excretion (gm/24 h)	Baseline / Increased UGE by the end of the trial period	20.3	21.4	14.0	13.4	-	-	-	-	-	-	-	15.2	16.9	21.1	14.9	-	-	-	-
	Change by the end of trial period	-3.3	72.8	103.1	101.5	-	-	-	-	-	-	-	<50	>100	>100	>100	-	-	-	-
	Comparison with placebo	-	76.1 (95% CI: 58.6, 93.6) p<0.001	106.4 (95% CI: ...) p<0.001	104.8 (95% CI: 88.9, 122.7) p<0.001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total insulin dose requirement per week (U/Kg)	Baseline	0.66	0.65	0.71	0.65	0.70	0.70	0.74	0.71	0.70	0.71	0.71	0.71	0.73	0.73	0.66	-	-	-	-
	Change by the end of trial period	-0.01	-0.08	-0.10	-0.09	-0.01	-0.09	-0.10	-0.01	-0.06	-0.08	-0.10	-0.07	-0.15	-0.17	-0.16	-	-	-	-
	Comparison with placebo	-	-0.07 (95% CI: -0.14, 0.00) p=0.044	-0.09 (95% CI: -0.16, -0.02) p=0.013	-0.08 (95% CI: -0.15, -0.01) p=0.023	-	-0.09 (95% CI: -0.11, -0.06) p<0.0001	-0.09 (95% CI: -0.12, -0.07) p<0.0001	-	-0.05 (95% CI: -0.07, -0.03) p<0.0001	-0.07 (95% CI: -0.09, -0.05) p<0.0001	-0.09 (95% CI: -0.11, -0.07) p<0.0001	-	-0.08 (95% CI: -0.16, -0.01) p=0.0245	-0.10 (95% CI: -0.17, -0.02) p=0.0112	-0.09 (95% CI: -0.16, -0.01) p=0.0202	-	-	-	-
Body weight (kg)	Baseline	79.8	75.9	87.1	76.9	83.4	86.2	85.7	80.7	81.6	83.8	83.3	63.64	63.26	59.88	60.54	-	-	-	-
	Change by the end of trial period	0.2	-1.4	-1.6	-1.7	0.2	-3.0	-3.4	0.2	-1.6	-2.8	-3.2	0.13	-1.24	-1.34	-1.57	-	-	-	-
	Comparison with placebo	-	-1.5 (95% CI: -2.4, -0.7) p<0.0001	-1.8 (95% CI: -2.7, -0.9) p<0.0001	-1.9 (95% CI: -2.7, -1.0) p<0.001	-	-3.2 (95% CI: -3.9, -2.5) p<0.0001	-3.6 (95% CI: -4.3, -2.8) p<0.0001	-	-1.8 (95% CI: -2.3, -1.2) p<0.0001	-3.0 (95% CI: -3.6, -2.5) p<0.0001	-3.4 (95% CI: -4.0, -2.9) p<0.0001	-	-1.37 (95% CI: -2.29, -0.44) p=0.0046	-1.47 (95% CI: -2.42, -0.52) p=0.0033	-1.70 (95% CI: -2.64, -0.75) p=0.0008	-	-	-	-
Systolic blood pressure (mmHg)	Baseline	124.4	122.0	121.8	124.4	124.7	124.0	124.9	120.4	123.4	125.1	124.5	116.6	114.1	110.1	115.8	129.9	134.5	132.4	129.9
	Change by the end of trial period	2.8	2.7	5.3	1.2	0.5	-2.9	-4.2	0.4	-1.7	-3.5	-3.4	3.7	-0.7	-4.6	3.4	2.5	7.3	6.5	5.1
	Comparison with placebo	-	p>0.05	p>0.05	p>0.05	-	-3.4 (95% CI: -5.6, -1.2) p=0.0024	-4.7 (95% CI: -6.9, -2.5) p<0.0001	-	-2.1 (95% CI: -3.9, -0.2) p=0.0270	-3.9 (95% CI: -5.7, -2.1) p<0.0001	-3.7 (95% CI: -5.6, -1.9) p<0.0001	-	-	-	-	-	p≥0.05	p≥0.05	p≥0.05
Diastolic blood pressure (mmHg)	Baseline	76.3	74.5	72.6	72.2	75.6	75.8	77.0	74.6	75.1	76.8	75.4	72.6	72.0	71.1	69.8	73.2	83.8	79.1	84.4
	Change by the end of trial period	2.7	1.3	3.9	2.2	-0.1	-1.8	-1.6	0.0	-0.4	-1.8	-1.5	1.6	-0.2	-2.7	1.5	-3.8	1.9	-0.7	10.7
	Comparison with placebo	-	p>0.05	p>0.05	p>0.05	-	-1.7 (95% CI: -3.1, -0.3) p=0.0168	-1.5 (95% CI: -2.9, -0.2) p=0.0290	-	-0.3 (95% CI: -1.5, 0.9) p=0.6023	-1.7 (95% CI: -2.9, -0.5) p=0.0047	-1.4 (95% CI: -2.6, -0.2) p=0.0202	-	-	-	-	-	p≥0.05	p≥0.05	p≥0.05
Total cholesterol (mmol/L)	Baseline	5.1	5.0	4.5	4.7															
	Change by the end of trial period	-0.3	0.1	0.3	0.1															
	Comparison with placebo	-																		
Low density lipoprotein (mmol/L)	Baseline	3.0	2.9	2.6	2.5															
	Change by the end of trial period	-0.3	0	0.3	0.2															
	Comparison with placebo	-																		
High density lipoprotein (mmol/L)	Baseline	1.5	1.5	1.5	1.8															
	Change by the end of trial period	0.0	0.1	0.0	-0.1															
	Comparison with placebo	-																		
Triglycerides (mmol/L)	Baseline	1.2	1.1	1.0	0.8															
	Change by the end of trial period	0.0	-0.1	0.2	0.0															
	Comparison with placebo	-																		

not reported/not applicable; EASE: Empagliflozin as an adjunctive to insulin therapy; HbA1c: Glycated hemoglobin; CI: Confidence interval; UGE: 24-hour urine glucose excretion.

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Table 4. Summary of safety data for the outcomes of interest.

Trial	Intervention	Ketoacidosis	Urinary tract infection	Limb amputation	Renal impairment	Fournier's gangrene	Bone fracture	Genital infection	Volume depletion related side effects	Study discontinuation of participants due to side effects
EASE 1 (38)	Empagliflozin 2.5 mg (n=19)	0	0	-	-	-	-	0	-	0
	Empagliflozin 10 mg (n=19)	0	0	-	-	-	-	0	-	0
	Empagliflozin 25 mg (n=18)	0	0	-	-	-	-	0	-	0
	Placebo (n=19)	0	0	-	-	-	-	0	-	0
EASE 2 and 3 (37)	Empagliflozin 10 mg (n=491)	21 (4.3)	47 (9.6)	0	1 (0.2)	-	14 (2.9)	63 (12.8)	12 (2.4)	29 (5.9)
	Empagliflozin 25 mg (n=489)	16 (3.3)	41 (8.4)	0	4 (0.8)	-	5 (1.0)	70 (14.3)	16 (3.3)	18 (3.7)
	Placebo (n=484)	6 (1.2)	41 (8.5)	0	3 (0.6)	-	8 (1.7)	21 (4.3)	8 (1.7)	14 (2.9)
EASE 3 (37)	Empagliflozin 2.5 mg (n=241)	2 (0.8)	13 (5.4)	1 (0.4)	0	-	5 (2.1)	13 (5.4)	1 (0.4)	8 (3.3)
Shimada et al., 2018 (39)	Empagliflozin 2.5 mg (n=13)	0	0	-	0	-	0	1 (7.7)	0	0
	Empagliflozin 10 mg (n=12)	0	0	-	0	-	0	0	0	0
	Empagliflozin 25 mg (n=12)	0	0	-	0	-	0	1 (8.3)	0	0
	Placebo (n=11)	0	0	-	0	-	0	0	0	0
Lunder et al., 2018 (40)	-	-	-	-	-	-	-	-	-	-

-not reported; EASE: Empagliflozin as an adjunctive to insulin therapy.

In the EASE 1 trial, a higher decrease was observed in the participants administered 10 mg (weekly decrease of 0.10 U/kg) and 25 mg (weekly decrease of 0.09 U/kg) groups, compared to the group administered 2.5 mg (weekly decrease of 0.08 U/kg) empagliflozin (38). In the EASE 3 trial, the reduction in insulin requirement among participants administered 25, 10, and 2.5 mg empagliflozin was 0.10, 0.08, and 0.06 U/kg, respectively (37). In the trial by Shimada et al., this decrease in groups administered 10 (weekly decrease of 0.17 U/kg) and 25 mg (weekly decrease of 0.16 U/kg) empagliflozin was higher than those given a dosage of 2.5 mg (weekly decrease of 0.15 U/kg) (39).

Bodyweight

A dose-dependent decrease in body weight was observed across all EASE trials (37,38) and the trial by Shimada et al. (39), and these reductions were statistically significant compared to the placebo.

Systolic blood pressure and diastolic blood pressure

In the EASE 2 and 3 trials, a dose-dependent decrease in the SBP and DBP was observed compared to the baseline, and the decrease was statistically significant compared to the placebo (37). In the EASE 1 trial, a decrease in the SBP and DBP from the baseline was observed in the 10 mg empagliflozin-treated arm; however, none of the empagliflozin dosages produced any statistically significant changes from the baseline when compared to the placebo (38). A small decrease in the SBP and DBP was observed in the group receiving 10 mg empagliflozin on days 7 & 28 in the study by Shimada et al. (39). The SBP and DBP did not change in the study by Lunder et al. even after intervention (40).

Lipid Profile

The lipid profile was reported only in the EASE 1 trial (38). A slight increase of 0.3 mmol/L in total cholesterol was observed in the group treated with 10 mg empagliflozin (38).

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A slight increase in LDL was observed in the group treated with 10 and 25 mg empagliflozin (0.3 and 0.2 mmol/L, respectively) (38).

Safety Profile

The burden of side effects occurring in the 25 and 10 mg empagliflozin treatment arms in the EASE 2 and 3 trials were reported in an aggregated form (37).

Ketoacidosis

In the EASE 2 and 3 trials, the highest number of ketoacidosis cases (4.3%) was observed in recipients of 10 mg empagliflozin. Among recipients of 25 and 2.5 mg empagliflozin users, this rate was 3.3% and 0.8%, respectively. In EASE 1 trial and that by Shimada et al., no diabetic ketoacidosis cases were reported (38,39).

Urinary Tract Infections (UTI)

In the EASE 2 and 3 trials, the frequency of UTI cases in recipients of 2.5, 10, and 25 mg was 5.4%, 9.6%, and 8.4%, respectively. In the EASE 1 trial (38), UTI was observed in a participant receiving 25 mg empagliflozin, while no UTI cases were recorded in the Japanese study (39).

Genital Infection

The frequency of genital infection increased in a dose-dependent manner. In the EASE 2 and 3 trials, these frequencies were 5.4%, 12.8%, and 14.3% in the 2.5, 10, and 25 mg empagliflozin treatment, respectively (37). In the EASE 1 trial, none of the participants had a genital infection (38). In the trial by Shimada et al., one case each was reported in the groups receiving 2.5 and 25 mg empagliflozin (39).

Volume Depletion-Related Side Effects

In the EASE 2 and 3 trials, the frequency of these side effects increased in a dose-dependent manner. In the 2.5, 10, and 25 mg empagliflozin treatment arms, these frequencies were 0.4, 2.4, and 3.3%, respectively (37). There were no such events in the trial by Shimada et al. (39).

Study discontinuation due to side effects
The study discontinuation due to side effects was relatively low (≤3% in EASE 2 and 3 trials) (37) or absent (38,39) among the trials that reported it.

Other Side Effects

Limb amputation was performed in a patient receiving 2.5 mg empagliflozin in the EASE 3 trial. Concerning bone fractures, in the EASE 2 and 3 trials, 14 events were observed in the 10 mg empagliflozin arm and 5 cases were reported in each of the 2.5 and 25 mg empagliflozin groups (37).

In the EASE 2 and 3 trials, almost 1.2% (3/241), 4.1% (20/491), and 2.7% (13/489) of severe hypoglycemia cases were observed in 2.5, 10, and 25 mg empagliflozin recipients, respectively (37). However, no such events were reported in the EASE 1 trial and the study by Shimada et al. (38,39).

Discussion

A total of 4 trials sourcing data from 1,870 T1DM patients of 45 nations were included in this review. In most of the trials, a decrease in the HbA1c levels, body weight, and total weekly insulin dose requirement was observed compared to baseline in a dose-dependent manner. Few trials reported a decline in the FPG from the baseline. The frequencies of the various side effects were relatively low.

Efficacy Outcomes

The effects of empagliflozin on SBP and DBP varied across the studies included herein. In some studies, a statistically significant decline in these parameters was observed in different empagliflozin treatment arms, whereas in others, no such effect was reported. In this regard, a single-arm clinical trial testing the effects of 25 mg empagliflozin over 8-weeks in T1DM patients reported a statistically significant decrease in SBP and no such change in DBP (16).

Several trials reviewed herein reported a decrease in the mean HbA1C, FPG, total weekly insulin requirement, and 24-hour urine glucose excretion from the baseline across different empagliflozin dosages, which was statistically significant compared to the placebo. A single-arm trial testing the effect of 25 mg empagliflozin therapy on these outcomes reported a statistically sig-

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nificant decrease in the effect after 8 weeks (14). However, we could not find similar single-arm trials testing the 2.5 and 10 mg dosages of empagliflozin on T1DM patients. Randomized double-blinded placebo-controlled trials testing the effects of 10 and 25 mg empagliflozin administered once-daily in T2DM patients also reported findings in line with some of the studies included in our review (41). Notably, a decrease in the SBP, DBP, and HbA1c levels was reported in this trial (41).

Safety Outcomes

Ketoacidosis

Regarding ketoacidosis, a recent update on SGLT2i medications reported its increased risk when used in T1DM patients (42). However, this empagliflozin-specific review suggests a minimal risk of ketoacidosis. Ketoacidosis was reported in 2 (37) of the four trials analyzing this factor (37-39). Even in those trials, the occurrence of ketoacidosis was minimal (<5% across all empagliflozin dosages) (Table 4). A recent meta-analysis suggested that SGLT2i do not have a dose-response relationship with the occurrence of diabetic ketoacidosis (43).

UTI

A meta-analysis comparing high- (10 mg) and low-dose (5 mg) dapagliflozin reported that the former had a lower risk of UTI (44). Although such a direct dose-wise meta-analysis was beyond the scope of our review, no UTI events were observed across different dosages of empagliflozin in two trials (38,39). In the remaining two trials, EASE 2 and 3, <10% of the participants in the respective treatment arms experienced UTI (37).

Genital infection

Aggregated data from different SGLT2i drugs tested in T1DM patients suggest that these drugs increase the risk of genital infection compared to placebo (28). Among the trials included in this review, genital infections mainly occurred in the EASE 2 and 3 trials (37). For larger dosages of empagliflozin (10 and 25 mg), the number of genital infection cases was higher than that of UTI and increased with the dose (37).

Overall safety profile

The adverse outcomes (i.e., ketoacidosis, UTI, genital infection, and study discontinuation) reported by EASE 1-3 (37,38) and Shimada et al. (39) were primarily observed in the EASE 2 and 3 trial. The possible reason might be that these 2 trials (37) had a larger sample size and a prolonged intervention duration than the other trials (38,39).

Other SGLTi

Due to the restricted nature of this review to a particular SGLT2i type, empagliflozin, exploring other variants of SGLT2i and combined SGLT2i and SGLT1i (e.g., sotagliflozin) were beyond the scope of this review. In this regard, a recent article (42) on the use of various SGLTi drugs in T1DM patients reported that SGLT2i leads to a reduction in the HbA1c levels and body weight. Our review on empagliflozin also suggests the same.

Strengths and Weakness

The key strength of this review is that it aggregated the information on the efficacy and safety of different empagliflozin doses in T1DM patients, based on epidemiologically rigorous evidence, i.e., randomized double-blinded controlled trials. Besides, the non-restricted nature of the database search to any language or geographical boundary highlights the comprehensiveness of this review. Furthermore, the incorporation of multicentric trials in this review ensures its applicability to a diverse population. Despite these strengths, this review also has a few weaknesses. Most of the trials (except for the EASE 2 and 3 trials) had a small sample size and were unlikely to have high statistical power. Besides, trials that reported the safety outcome data limited their reporting to frequency data only. Therefore, a statistical comparison with the placebo was not available. Furthermore, due to the qualitative nature of this review, we could not derive the statistical summaries of the different efficacy and safety-related outcomes.

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Conclusion

A dose-dependent decrease in the HbA1c levels, body weight, and total weekly insulin dose requirement was observed in most of the randomized controlled trials testing empagliflozin in T1DM patients. The occurrence of ketoacidosis, UTI, and study discontinuation due to side effects was rare in empagliflozin-treated T1DM patients. Genital infection predominantly occurred at higher empagliflozin dosages (i.e., 10 and 25 mg).

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sumanta Saha; Design: Sumanta Saha, Sujata Saha; Control/Supervision: Sumanta Saha; Data Collection and/or Processing: Sumanta Saha, Sujata Saha; Analysis and/or Interpretation: Sumanta Saha, Sujata Saha; Literature Review: Sumanta Saha, Sujata Saha; Writing the Article: Sumanta Saha, Sujata Saha; Critical Review: Sumanta Saha, Sujata Saha.

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