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NEPHROLOGY - REVIEW

Effect of sodium–glucose cotransporter 2 inhibitors on hemoglobin and hematocrit levels in type 2 diabetes: a systematic review and meta-analysis

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Abstract

Background Sodium–glucose cotransporter 2 inhibitors (SGLT2i) improve outcomes of patients with type 2 diabetes at high cardiovascular risk and chronic kidney disease. Recent studies showed an increase in hemoglobin and hematocrit after SGLT2i treatment.

Materials and methods We did a systematic review and meta-analysis of randomized, double-blind, placebo-controlled studies of SGLT2i in patients with type 2 diabetes. We searched through PubMed/Medline, Web of Science, Embase (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley) from January 2010 to January 2021.

Results We included seventeen randomized, double-blind, placebo-controlled studies. The total number of evaluated patients was 14,748. The treatment arm consisted of canagliflozin, dapagliflozin, empagliflozin and ipragliflozin. SGLT2i therapy significantly increased hemoglobin levels when compared to placebo (MD 5.60 g/L, 95% CI 3.73–7.47 g/L, $P < 0.00001$, considerable heterogeneity—$I^2 = 94\%$). Each SGLT2i also led to a significant increase in the hematocrit level when compared to placebo (MD 1.32%, 95% CI 1.21–1.44, $P < 0.00001$, considerable heterogeneity—$I^2 = 99\%$).

Conclusions SGLT2i led to significant increases in hemoglobin and hematocrit levels when compared to placebo. In addition to their cardiovascular effect, SGLT2i also increases hemoglobin and hematocrit levels.

Keywords SGLT2 inhibitors · Anemia · Diabetes mellitus · Dapagliflozin · Canagliflozin · Empagliflozin · Ipragliflozin

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Introduction

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are a class of glucose-lowering drugs that increase urinary glucose excretion by inhibiting glucose reabsorption in the proximal tubule. SGLT2i decrease blood pressure and blood glucose levels and contribute to weight loss [1, 2]. There is also strong evidence demonstrating the cardioprotective and renoprotective effects of this class of glucose-lowering drugs. Different mechanisms are thought to contribute to organ protection, including the activation of tubuloglomerular feedback leading to reduced intraglomerular pressures, diuresis, lower blood pressure, and weight loss [1–3]. They also impact anti-inflammatory pathways which may contribute to cardiorenal protection [1, 2].

Anemia worsens the prognosis of many diseases such as type 2 diabetes mellitus and chronic kidney disease leading to increased morbidity and mortality [4–6]. Kidneys have regulatory effects on red blood cell production through

erythropoietin release in response to hypoxia [7]. Type 2 diabetes mellitus is a major risk factor for chronic kidney disease, which can potentially lead to anemia development. Previous studies have reported an increase in hemoglobin and hematocrit levels with the initiation of SGLT2i in type 2 diabetes mellitus patients [8–11]. Although this could be explained by a decrease in plasma volume leading to hemoconcentration, additional mechanisms may contribute to the increase in hemoglobin and hematocrit values following the administration of SGLT2i [8, 12]. There are also reports explaining the relationship between SGLT2i and increased red blood cell parameters [9, 11–13]. In this meta-analysis, we investigate the effects of different SGLT2i administered in varying doses on hemoglobin and hematocrit levels in type 2 diabetes mellitus patients.

Methods

Our study investigated the impact of SGLT2i on hemoglobin and hematocrit levels. We selected the included studies from various databases according to predefined inclusion and exclusion criteria. We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines to report this meta-analysis (Supplementary Table S1).

Literature search and inclusion/exclusion criteria

In this systematic review and meta-analysis, we performed a literature search through four databases, including PubMed/Medline, Web of Science, Embase (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley) from January 2010 to January 2021 using the following keywords: ''SGLT2i'', ''SGLT2 inhibitor'', ''type 2 diabetes mellitus'', ''hematocrit'', ''hemoglobin'', ''anemia", "cardiovascular disease", "chronic kidney disease", and "hypoxia-inducible factor".

We independently assessed the titles and the abstracts of each study. We discussed and reexamined each article in detail until reaching a consensus if any conflicts were present. We also analyzed the references of all selected studies. After the preliminary selection, we independently evaluated the full-text versions of the selected studies.

The inclusion criteria for our systematic review and meta-analysis were as follows: we included studies that provided data on SGLT2i and red blood cell parameters, hemoglobin and hematocrit levels. Studies with retrospective or prospective design irrespective of randomization were included and cross-sectional studies were excluded. All included studies were in English and published in a peer-reviewed journal until January 2021.

We excluded studies with missing data or inadequate description of outcomes. Studies not classified as original articles (e.g. reviews, meta-analyses, editorials, commentaries), study designs that were not listed in our inclusion criteria (e.g. case reports, case series), and unpublished data were also excluded from our study. Our search algorithm is presented in Fig. 1.

Quality assessment

We assessed the quality of each included study in accordance with the Newcastle–Ottawa Scale [14] which uses the selection of study groups as the main criteria, assessment of outcomes, and comparability of the groups (Tables 1, 2). The Newcastle–Ottawa Scale scores a study out of nine stars, the maximum score representing the highest quality research [14]. We reached a consensus decision on the quality assessment of each study.

We used the Cochrane risk-of-bias tool for the risk of bias assessment in the included studies (supplementary table 2). The Cochrane risk-of-bias tool was used to evaluate randomization, masking of treatment allocation, blinding, adherence and withdrawals for each of the randomized controlled trials [15].

Statistical analysis

We used a random-effects model in an inverse variance analysis and expressed treatment effects as mean difference (MD) for continuous outcomes with 95% CI (hemoglobin, hematocrit). Treatment effect was significant if $P < 0.05$. When the results were expressed as standard error, we converted standard error to standard deviation using a standard formula [16].

We used the I^2 statistic to assess inconsistency across individual studies [17]. An $I^2 > 50\%$ indicated a large heterogeneity which was not explained by chance.

If a sufficient number of studies were identified, subgroup analysis was used to explore possible sources of heterogeneity. All statistical analyses were performed using Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration 2012).

Results

We included, in our final analysis, seventeen randomized, double-blind, placebo-controlled studies [9–11, 18–31] (Tables 1, 2). The total number of evaluated patients was 14,748 (with a minimum of 180 [21] and a maximum of 7020 patients [31]). All studies enrolled type 2 diabetes patients. Estimated glomerular filtration rate was above 30 ml/min/1.73 m^2 in all studies. The treatment arm

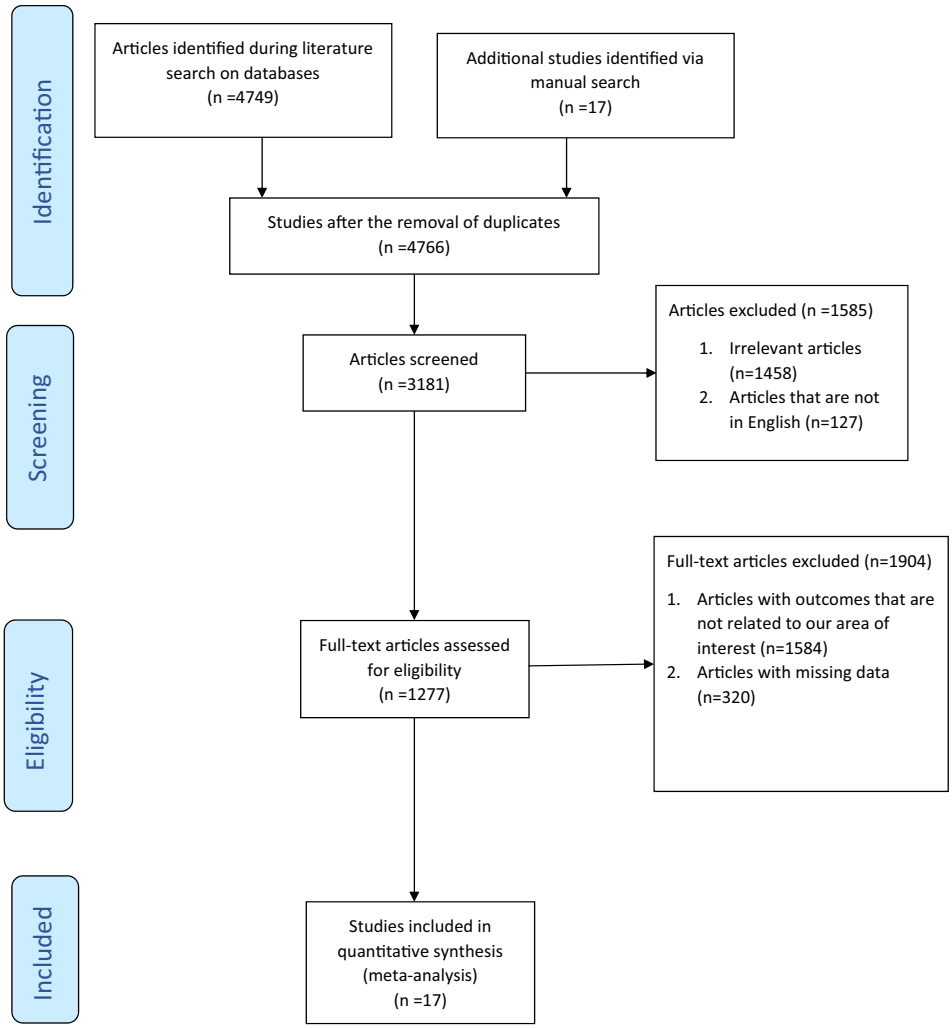

Fig. 1 Flow diagram of the study selection process

consisted of canagliflozin [13, 22, 25, 27, 30], dapagliflozin [10, 11, 19–21, 23, 24, 29], empagliflozin [9, 18, 31] and ipragliflozin [28]. The doses of the different SGLT2i were as follows: canagliflozin 50 mg [13], 100 mg [22, 25, 27, 30], 200 mg [13], 300 mg [13, 22, 25, 27, 30] and 300 mg [13]; dapagliflozin 1 mg [11, 24], 2.5 mg [10, 11, 19, 20, 23, 24, 30], 5 mg [10, 11, 19, 20, 23, 24, 29], 10 mg [10, 19–21, 23, 24, 29], and 20 mg and 50 mg [10]; empagliflozin 10 mg and 25 mg [9, 18, 31]; ipragliflozin 12.5 mg, 50 mg, 150 mg and 300 mg [28].

All the included studies reported the outcomes as MD between baseline and post-intervention values measured at different timings across the study (at 12 weeks [10, 13, 24, 28], at 24 weeks [9, 11, 18–21, 23], at 26 weeks [22, 27, 30], at 48 weeks [29, 31] and at 52 weeks [25].

We evaluated all the included studies in terms of the risk of bias using the Cochrane risk of bias tool (supplementary table 2). All of the studies were double-blind trials. Seven of the included studies did not report the details of allocation concealment. There were no incomplete outcomes and selective reporting in the seventeen studies.

Outcome measures reporting

Effect of SGLT2i on hemoglobin

There were seven studies, five with canagliflozin [13, 22, 25, 27, 30], one with empagliflozin [31] and one with ipragliflozin [28] that evaluated the effect of SGLT2i therapy on hemoglobin levels. As shown in Fig. 2, SGLT2i therapy was shown to significantly increase hemoglobin when compared to placebo (MD 5.60 g/L, 95% CI 3.73–7.47 g/L, $P < 0.00001$, considerable heterogeneity—$I^2 = 94\%$) at 12–48 weeks of follow-up. Given the large heterogeneity, we, therefore, analyzed the effect on hemoglobin levels by SGLT2i class. As shown in Fig. 3, empagliflozin, canagliflozin and ipragliflozin all significantly increased hemoglobin levels, with a trend for a further increase in hemoglobin

Table 1 Characteristics of the studies of which investigated hematocrit changes included in this meta-analysis

Study name	Study design	Single-/multi-center	Type of SGLT2i dose	*n*	Average age (years)	Gender, male (*n* (%))	Follow-up (weeks)	Hematocrit level at baseline (%) (SD); change in hematocrit (%) (SD)	Change in hematocrit	Quality assessment (Newcastle–Ottawa)
List et al. [10]	RCT	Multicenter	Dapagliflozin 2.5 mg/day	59	55 ± 11	29 (49%)	12	ND; + 1.51 (2.12)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 5 mg/day	58	55 ± 12	28 (48%)		+ 2.03 (2.36)	Increase	
			Dapagliflozin 10 mg/day	47	54 ± 9	25 (53%)		+ 1.95 (2.19)	Increase	
			Dapagliflozin 20 mg/day	59	55 ± 10	32 (54%)		+ 2.57 (2.44)	Increase	
			Dapagliflozin 50 mg/day	56	53 ± 10	25 (45%)		+ 2.86 (2.75)	Increase	
			Placebo	54	53 ± 11	30 (56%)		− 0.08 (2.16)	Decrease	
			Metformin	56	54 ± 9	27 (48%)		− 1.12 (2.62)	Decrease	
Bailey et al. [20]	RCT	Multicenter	Dapagliflozin 2.5 mg/day	137	55.0 ± 9.3	70 (51%)	24	42.4 (4·0) + 1.0 (0.2)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 5 mg/day	137	54.3 ± 9.4	69 (50%)		42.1 (3.6) + 1.3 (0.2)	Increase	
			Dapagliflozin 10 mg/day	135	52.7 ± 9.9	77 (57%)		42.8 (4.0) + 1.7 (0.2)	Increase	
			Placebo	137	53.7 ± 10.3	76 (55%)		42.6 (3.9) − 1.1 (0.2)	Decrease	
Ferrannini et al. [23]	RCT	Multicenter	Dapagliflozin 2.5 mg/day	65	53.0 ± 11.7	36 (55%)	24	+ 1.60 (0.33)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 5 mg/day	64	52.6 ± 10.9	31 (48%)		+ 1.74 (0.40)	Increase	
			Dapagliflozin 10 mg/day	70	50.6 ± 10.0	34 (49%)		+ 2.38 (0.44)	Increase	
			Placebo	75	52.7 ± 10.3	31 (41%)		− 0.38 (0.25)	Decrease	

Table 1 (continued)

Study name	Study design	Single-/multi-center	Type of SGLT2i dose	*n*	Average age (years)	Gender, male (*n* (%))	Follow-up (weeks)	Hematocrit level at baseline (%) (SD); change in hematocrit (%) (SD)	Change in hematocrit	Quality assessment (Newcastle–Ottawa)
Strojek et al. [19]	RCT	Multicenter	Dapagliflozin 2.5 mg/day + open-label glimepiride 4 mg/day	154	59.9 ± 10.14	77 (50%)	24	41.97 (4.11) + 1.93 [0.20]	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 5 mg/day + open-label glimepiride 4 mg/day	142	60.2 ± 9.73	71 (50%)		41.98 (3.23) + 2.28 [0.22]	Increase	
			Dapagliflozin 10 mg/day + open-label glimepiride 4 mg/day	151	58.9 ± 8.32	66 (44%)		42.25 (3.72) + 2.19 [0.20]	Increase	
			Placebo + open-label glimepiride 4 mg/day	145	60.3 ± 10.16	71 (49%)		41.83 (3.47) + 0.01 [0.17]	Increase	
Bailey et al. [11]	RCT	Multicenter	Dapagliflozin 1 mg/day	72	53.7 ± 9.0	38 (53%)	24	43.18 (3.25) + 0.62 (0.38)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 2.5 mg/day	74	53.5 ± 10.6	34 (46%)		43.26 (3.92) + 1.33 (0.33)	Increase	
			Dapagliflozin 5 mg/day	68	51.3 ± 11.5	32 (47%)		42.72 (3.82) + 1.77 (0.29)	Increase	
			Placebo	68	53.5 ± 11.1	37 (54%)		43.70 (3.86) − 0.72 (0.28)	Decrease	

Table 1 (continued)

Study name	Study design	Single-/multi-center	Type of SGLT2i dose	*n*	Average age (years)	Gender, male (*n* (%))	Follow-up (weeks)	Hematocrit level at baseline (%) (SD); change in hematocrit (%) (SD)	Change in hematocrit	Quality assessment (Newcastle–Ottawa)
Rosenstock et al. [13]	RCT	Multicenter	Canagliflozin 50 mg/day	64	53.3 ± 8.5	34 (53%)	12	+ 1.11 (0.38)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 100 mg/day	64	51.7 ± 8.0	36 (56%)		+ 2.33 (0.35)	Increase	
			Canagliflozin 200 mg/day	65	52.9 ± 9.6	33 (51%)		+ 2.09 (0.39)	Increase	
			Canagliflozin 300 mg/day	64	52.3 ± 6.9	36 (56%)		+ 2.37 (0.43)	Increase	
			Canagliflozin 300 mg BID	64	55.2 ± 7.1	28 (44%)		+ 2.60 (0.40)	Increase	
			Sitagliptin 100 mg/day	65	51.7 ± 8.1	38 (58%)		− 0.75 (0.35)	Decrease	
			Placebo	65	53.3 ± 7.8	31 (48%)		− 0.04 (0.32)	Decrease	
Wilding et al. [28]	RCT	Multicenter	Ipragliflozin 12.5 mg/day	69	56.6 ± 8.5	33 (48%)	12	+ 0.01 (0.02)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Ipragliflozin 50 mg/day	68	58.6 ± 7.6	32 (47%)		+ 0.02 (0.02)	Increase	
			Ipragliflozin 150 mg/day	67	58.1 ± 8.2	38 (57%)		+ 0.03 (0.03)	Increase	
			Ipragliflozin 300 mg/day	72	56.6 ± 8.9	36 (50%)		+ 0.02 (0.02)	Increase	
			Placebo	66	57.3 ± 8.6	36 (54%)		+ 0.0 (0.02)	No effect	
Wilding et al. [29]	RCT	Multicenter	Dapagliflozin 2.5 mg + Insulin	202	59.8 ± 7.6	100 (49%)	48	40.83 (3.78) + 1.92 (2.63)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 5 mg + Insulin	211	59.3 ± 7.9	100 (47%)		41.25 (3.80) + 2.39 (2.31)	Increase	
			Dapagliflozin 10 mg + Insulin	194	59.3 ± 8.8	87 (45%)		41.34 (3.90) + 2.63 (2.70)	Increase	
			Placebo + Insulin	193	58.8 ± 8.6	95 (49%)		41.75 (3.58) + 0.12 (2.07)	Increase	

Table 1 (continued)

Study name	Study design	Single-/multi-center	Type of SGLT2i dose	*n*	Average age (years)	Gender, male (*n* (%))	Follow-up (weeks)	Hematocrit level at baseline (%) (SD); change in hematocrit (%) (SD)	Change in hematocrit	Quality assessment (Newcastle–Ottawa)
Bolinder et al. [21]	RCT	Multicenter	Dapagliflozin 10 mg/day + metformin	89	60.6 ± 8.2	49 (55%)	24	42.1 (3.1) + 2.59 (0.30)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Placebo + metformin	91	60.8 ± 6.9	51 (56%)		42.1 (3.5) − 0.39 (0.20)	Decrease	
Haring et al. [18]	RCT	Multicenter	Empagliflozin 10 mg/day	225	57.0 ± 9.2	113 (50%)	24	42.2 (4.1) + 2.7 (3.4)	increase	Selection: 3 Comparability: 2 Exposure: 3
			Empagliflozin 25 mg/day	216	57.4 ± 9.3	114 (53%)		41.8 (5.0) + 2.5 (3.4)	increase	
			Placebo	225	56.9 ± 9.2	112 (50%)		41.7 (4.3) − 0.8 (3.1)	decrease	
Kaku et al. [24]	RCT	Multicenter	Dapagliflozin 1 mg/day	59	55.9 ± 9.7	47 (80%)	12	+ 0.76 (0.27)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Dapagliflozin 2.5 mg/day	56	57.7 ± 9.3	39 (70%)		+ 1.53 (0.30)	Increase	
			Dapagliflozin 5 mg/day	58	58.0 ± 9.5	47 (81%)		+ 1.76 (0.28)	Increase	
			Dapagliflozin 10 mg/day	52	56.5 ± 11.5	39 (75%)		+ 2.07 (0.31)	Increase	
			Placebo	54	58.4 ± 10.0	43 (80%)		− 0.59 (0.27)	Decrease	
Zinman et al. [31]	RCT	Multicenter	Empagliflozin 10 mg/day	2345	63.0 ± 8.6	1653 (70.5%)	48	41.2 (5.6) + 4.8 (5.5)	İncrease	Selection: 3 Comparability: 2 Exposure: 3
			Empagliflozin 25 mg	2342	63.2 ± 8.6	1683 (71.9%)		41.3 (5.7) + 5.0 (5.3)	İncrease	
			Placebo	2333	63.2 ± 8.8	1680 (72.0%)		41.1 (5.7) + 0.9 (4.7)	İncrease	
Kovacs et al. [9]	RCT	Multicenter	Empagliflozin 10 mg/day	165	54.7 ± 9.9	83 (50%)	24	41.6 (5.0) + 2.1 (4.4)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Empagliflozin 25 mg/day	168	54.2 ± 8.9	85 (51%)		40.6 (5.2) + 2.6 (3.4)	Increase	
			Placebo	165	54.6 ± 10.5	73 (44%)		40.6 (4.9) − 0.6 (3.6)	Decrease	

Table 1 (continued)

Study name	Study design	Single-/multi-center	Type of SGLT2i dose	*n*	Average age (years)	Gender, male (*n* (%))	Follow-up (weeks)	Hematocrit level at baseline (%) (SD); change in hematocrit (%) (SD)	Change in hematocrit	Quality assessment (Newcastle–Ottawa)
Yale et al. [30]	RCT	Multicenter	Canagliflozin 100 mg/day	90	69.5 ± 8.2	58 (64%)	26	40.1 + 6.0 (7.6)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 300 mg/day	89	67.9 ± 8.2	48 (54%)		39.2 + 4.8 (6.9)	Increase	
			Placebo	90	68.2 ± 8.4	57 (63%)		40.8 − 0.1 (9.1)	Decrease	

SGLT2i sodium–glucose cotransporter 2 inhibitors, *RCT* randomized, double-blind, placebo-controlled trial, *M* male, *n* number, *SD* standard deviation, *ND* no data

for empagliflozin (MD 6.24 g/L, 95% CI 3.08–9.40, $P < 0.00001$, significant heterogeneity—$I^2 = 98\%$).

When analyzing separately the studies in which canagliflozin was administered, no significant differences were observed between the 100 mg and the 300 mg (MD = − 0.25 g/L, 95% CI − 0.91–0.41, $P = 0.46$, reduced heterogeneity—$I^2 = 7\%$) [13, 22, 25, 27].

Therefore, the large heterogeneity may be explained by the use of different molecules at different doses. Moreover, the included patients had different baseline eGFR, varying from normal renal function to stage 3 CKD. Another possible explanation is represented by the fact that none of the included studies was originally designed to assess the impact of SGLT2i on hemoglobin levels. The follow-up periods were also different and the effect may be time-dependent.

Effect of SGLT2i on hematocrit

In total, thirteen studies reported the mean change in hematocrit level after treatment with SGLT2i: eight with dapagliflozin [10, 11, 19–21, 23, 24, 29], two with canagliflozin [13, 30], three with empagliflozin [9, 18, 31] and one with ipragliflozin [28]. SGLT2i treatment was significantly associated with increased hematocrit levels when compared to placebo (MD 1.32%, 95% CI 1.21–2.44, $P < 0.00001$, considerable heterogeneity—$I^2 = 99\%$) (Fig. 4) at 12–48 weeks of follow-up.

When analyzed individually, each SGLT2i led to a significant increase in the hematocrit level when compared to placebo (MD 2.19%, 95% CI 0.28–4.10, $P < 0.00001$, considerable heterogeneity—$I^2 = 100\%$) (Fig. 5) at 12–48 weeks of follow-up.

To determine whether there was a dose-dependent effect, we then analyzed each SGLT2i by dose.

For dapagliflozin, the 2.5 mg was non inferior to the 5 mg dose (MD 0.00%, 95% CI 0.00–0.01, $P = 0.07$, insignificant heterogeneity—$I^2 = 0\%$), but inferior to the 10 mg dose (MD 0.34%, 95% CI 0.00–0.67, $P = 0.05$, moderate heterogeneity—$I^2 = 55\%$) (Supplementary Fig. 1) [10, 11, 19, 20, 23, 24, 29]. Additionally, there were six studies [10, 19, 20, 23, 24, 29] which compared the 5 mg with the 10 mg. This analysis showed no significant difference in hematocrit levels with the 10 mg dose (MD 0.00%, 95% CI 0.00–0.41, $P = 0.37$, insignificant heterogeneity—$I^2 = 0\%$).

For canagliflozin, there was no significant difference between the doses of 100 mg and the 300 mg, in the two studies that reported data on hematocrit (MD − 0.12%, 95% CI − 0.97–0.73, $P = 0.78$, insignificant heterogeneity—$I^2 = 0\%$) [13, 30].

Similarly, no significant dose-dependent effect was noted with the 25 mg of empagliflozin, when compared to the 10 mg (MD 0.20%, 95% CI − 0.08–0.48, $P = 0.99$, insignificant heterogeneity—$I^2 = 0\%$) [9, 31].

Table 2 Characteristics of the studies of which investigated hemoglobin changes included in this meta-analysis

Study name	Study design	Single-multicenter	SGLT2i dose	*n*	Average age (years)	Gender, male (*n*, (%))	Follow-up (weeks)	Hemoglobin *t* level at baseline (g/L) (SD); change in hemoglobin (g/L) (SD)	Change in hemoglobin levels	Quality assessment (Newcastle–Ottawa)
Rosenstock et al. [13]	RCT	Multicenter	Canagliflozin 50 mg/day	64	53.3 ± 8.5	34 (53%)	12	+ 3.2 (0.90)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 100 mg/day	64	51.7 ± 8.0	36 (56%)		+ 5.6 (0.90)	Increase	
			Canagliflozin 200 mg/day	65	52.9 ± 9.6	33 (51%)		+ 6.0 (0.90)	Increase	
			Canagliflozin 300 mg/day	64	52.3 ± 6.9	36 (56%)		+ 5.9 (1.36)	Increase	
			Canagliflozin 300 mg BID	64	55.2 ± 7.1	28 (44%)		+ 8.1 (1.01)	Increase	
			Sitagliptin 100 mg/day	65	51.7 ± 8.1	38 (58%)		− 2.7 (0.92)	Decrease	
			Placebo	65	53.3 ± 7.8	31 (48%)		− 0.7 (0.78)	Decrease	
Wilding et al. [28]	RCT	Multicenter	Ipragliflozin 12.5 mg/day	69	56.6 ± 8.5	33 (48%)	12	+ 3.3 (6.7)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Ipragliflozin 50 mg/day	68	58.6 ± 7.6	32 (47%)		+ 4.3 (7.7)	Increase	
			Ipragliflozin 150 mg/day	67	58.1 ± 8.2	38 (57%)		+ 7.6 (10.2)	Increase	
			Ipragliflozin 300 mg/day	72	56.6 ± 8.9	36 (50%)		+ 4.8 (8.0)	Increase	
			Placebo	66	57.3 ± 8.6	36 (54%)		+ 0.4 (6.1)	Increase	
Bode et al. [22]	RCT	Multicenter	Canagliflozin 100 mg/day	241	64.3 ± 6.5	124 (51%)	26	139.9 + 3.99 (6.1)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 300 mg/day	236	63.4 ± 6.0	129 (55%)		139.1 + 4.3 (6.2)	Increase	
			Placebo	237	63.2 ± 6.2	143 (60%)		138.9 + 0.7 (5.5)	Increase	
Lavalle-Gonzalez et al. [25]	RCT	Multicenter	Canagliflozin 100 mg/day	368	55.5 ± 9.4	174 (47%)	26	141.0 − 1.6 (6.2)	Decrease	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 300 mg/day	367	55.3 ± 9.2	165 (45%)		140.5 + 4.0 (7.2)	increase	
			Sitagliptin 100 mg/day	366	55.5 ± 9.6	172 (47%)		140.0 + 3.7 (7.1)	Increase	
			Placebo	183	55.3 ± 9.8	94 (51%)		141.3 − 1.6 (6.0)	Decrease	

Table 2 (continued)

Study name	Study design	Single-multicenter	SGLT2i dose	*n*	Average age (years)	Gender, male (*n*, (%))	Follow-up (weeks)	Hemoglobin *t* level at baseline (g/L) (SD); change in hemoglobin (g/L) (SD)	Change in hemoglobin levels	Quality assessment (Newcastle–Ottawa)
Stenlof et al. [27]	RCT	Multicenter	Canagliflozin 100 mg/day	195	55.1 ± 10.8	81 (41%)	26	143.3 + 3.9 (6.0)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 300 mg/day	197	55.3 ± 10.2	89 (45%)		145.0 + 3.6 (5.4)	Increase	
			Placebo	192	55.7 ± 10.9	88 (46%)		143.8 − 0.2 (6.5)	Decrease	
Yale et al. [30]	RCT	Multicenter	Canagliflozin 100 mg/day	90	69.5 ± 8.2	58 (64%)	26	133.8 + 5.3 (7.4)	Increase	Selection: 3 Comparability: 2 Exposure: 3
			Canagliflozin 300 mg/day	89	67.9 ± 8.2	48 (54%)		130.9 + 3.1 (5.9)	Increase	
			placebo	90	68.2 ± 8.4	57 (63%)		136.2 − 0.5 (8.1)	Decrease	
Zinman et al. [31]	RCT	Multicenter	Empagliflozin 10 mg/day	2345	63.0 ± 8.6	1653 (70.5%)	48	134 (1.5) + 8 (1.3)	İncrease	Selection: 3 Comparability: 2 Exposure: 3
			Empagliflozin 25 mg	2342	63.2 ± 8.6	1683 (71.9%)		135 (1.5) + 8 (1.3)	İncrease	
			Placebo	2333	63.2 ± 8.8	1680 (72.0%)		134 (1.5) − 1 (1.2)	Decrease	

SGLT2i sodium–glucose cotransporter 2 inhibitors, *RCT* randomized, double-blind, placebo-controlled trial; *n* number, *SD* standard deviation, *ND* no data

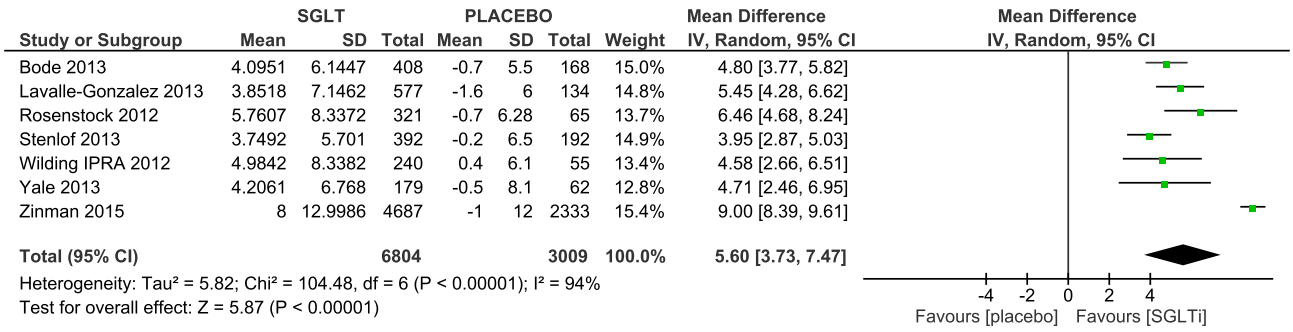

Fig. 2 The effect of sodium–glucose cotransporter 2 inhibitors on hemoglobin level

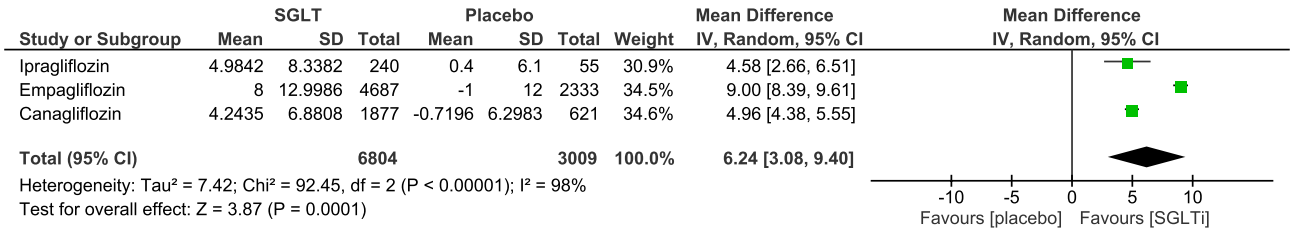

Fig. 3 The group effect of sodium–glucose cotransporter 2 inhibitors on hemoglobin level

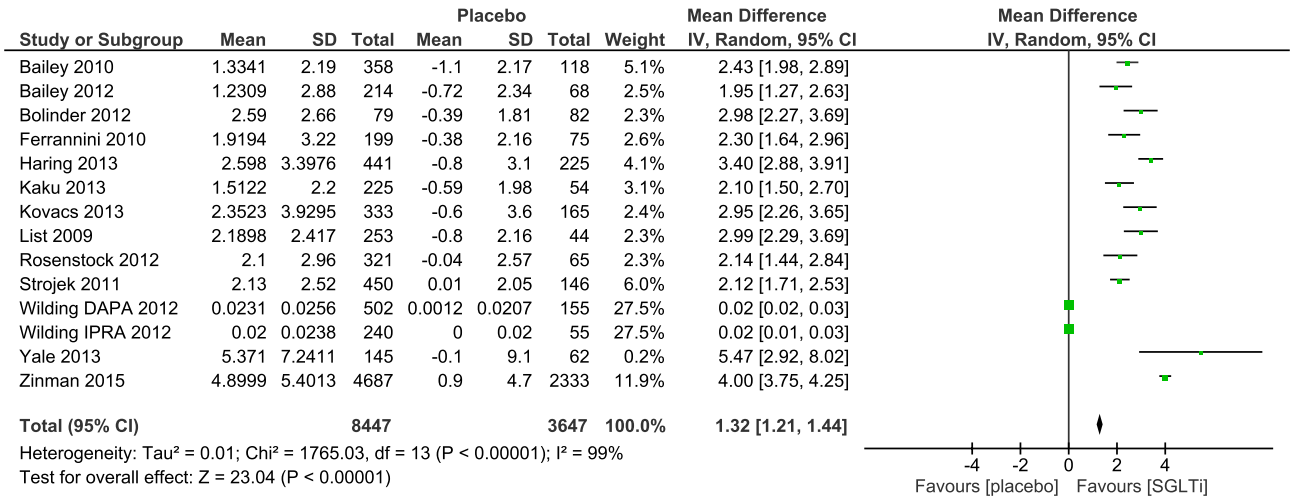

Fig. 4 The effect of sodium–glucose cotransporter 2 inhibitors on hematocrit level

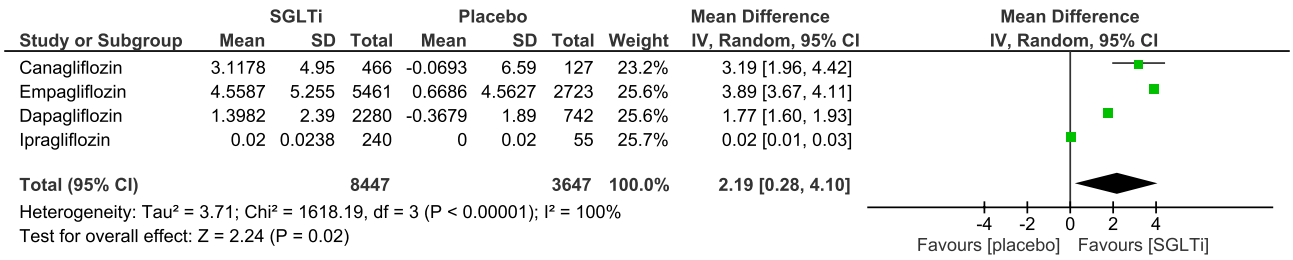

Fig. 5 The group effect of sodium–glucose cotransporter 2 inhibitors on hematocrit level

Discussion

In this systematic review and meta-analysis, we investigated the effects of different types and doses of SGLT2i on hemoglobin and hematocrit levels. The treatment arm consisted of canagliflozin [13, 22, 25, 27, 30], dapagliflozin [10, 11, 19–21, 23, 24, 29], empagliflozin [9, 18, 31] and ipragliflozin [28]. We showed that hemoglobin and hematocrit levels were significantly increased with SGLT2i therapy when compared to placebo.

In addition to their glucose-lowering effects, SGLT2i reduce blood pressure levels and contribute to weight loss [1, 2]. SGLT2i exert these effects through several mechanisms such as the activation of tubuloglomerular feedback leading to decreased intraglomerular pressures and diuresis leading to calorie and sodium losses [32]. They also have anti-inflammatory effects and reduce the fibrotic, and hyperplastic responses of proximal tubular cells through the prevention of hyperfiltration and glucose reabsorption in the renal proximal tubule [32].

Previous studies have shown that anemia worsens the prognosis of many diseases such as type 2 diabetes mellitus, chronic kidney disease, chronic heart failure, chronic obstructive pulmonary disease, thus leading to increased morbidity and mortality [4, 33]. In this analysis, SGLT2i therapies raise hemoglobin and hematocrit levels [8], an effect that has been linked with cardiorenal protection, possibly by improving tissue oxygen delivery. The rise in hemoglobin and hematocrit could be partially explained by a decrease in plasma volume due to the diuretic effects of SGLT2i. Among the included studies Bailey et al. [11], Rosenstock et al. [13] and Kovacs et al. [9] have all argued that the increase in hematocrit and hemoglobin levels could be explained by circulating volume contraction effects of SGLT-2i.

In contrast, several studies implied that other mechanisms engaged by SGLT2i could explain the increase in hemoglobin and hematocrit levels, besides volume depletion [30]. One postulated mechanism would be the correction of pathologically decreased erythropoietin levels. Erythropoietin is a hormone synthesized mainly by renal interstitial fibroblasts, in an oxygen-dependent manner, via hypoxia-inducible factor (HIF) [8, 34]. Glucose is cotransported with sodium (Na^+) ions via SGLT2 channels located on proximal renal tubules [12]. This process is highly dependent on the Na^+ ion gradient between tubule lumen and renal proximal tubular cells [12]. The Na^+ ion gradient is maintained by Na^+/K^+/ATPase channels consuming a significant amount of ATP [12]. In patients with type 2 diabetes, higher amounts of glucose are reabsorbed causing increased stress in renal interstitial cells due to relative depletion of oxygen levels, as most are consumed by the proximal renal tubular epithelium [12]. This causes ischemia and further fibrosis of renal interstitial cells, leading to decreased erythropoietin levels, which could explain anemia in patients with kidney diseases [12]. SGLT2i could prevent damage to the renal interstitial cells by reducing the activity of SGLT2 channels on proximal tubular cells, which would result in the preservation of adequate erythropoietin levels and subsequent increase in hemoglobin and hematocrit levels [12]. In any case, this hypothesis is marred by the fact that hypoxia would acutely induce erythropoietin synthesis and the effects of SGLT2i on hemoglobin occurred relatively early [35].

SGLT2 may also have direct effects on HIF metabolism. The two types of HIFs: HIF-1α or HIF-2α, although similar, possess different cellular actions and distribution patterns. Indeed, these two isoforms often have opposing actions. While HIF-1α decreases oxygen use and increases angiogenesis, HIF-2α is the primary stimulus for erythropoietin synthesis. It was suggested that SGLT2i inhibit HIF1α, but may increase SIRT1-mediated activation of HIF-2α [36]. Thus, SGLT2i may increase erythropoietin secretion directly and indirectly by decreasing renal fibrosis and enhancing the viability of erythropoietin secreting cells. Indeed, a recent study has shown that HIF-1α is the therapeutic target of SGLT2i for diabetic kidney disease and tubulointerstitial fibrosis [37].

Last but not least, there are also studies that showed that the anti-inflammatory actions of SGLT2i may contribute to increase hemoglobin and hematocrit. Dapagliflozin reduced circulating hepcidin and ferritin concentrations while increasing levels of the hepcidin inhibitor erythroferrone, and transiently increasing erythropoietin. Additionally, dapagliflozin increased plasma transferrin levels and expression of transferrin receptors 1 and 2 but there was no change in the expression of the iron cellular transporter, ferroportin [38].

The important question is that to what extent these different mechanisms contribute to hemoglobin and hematocrit elevation. In fact, the mechanisms by which SGLT2 inhibitors improve hemoglobin levels in patients with diabetes and chronic kidney disease are not fully understood and there are also other suggested mechanisms. For example, it is postulated that SGLT2i have diuretic-like effects and reduce plasma volume (a probable cause of hemoconcentration and hemoglobin elevation) and increase EPO secretion by renal fibroblasts [39]. In addition, SGLT2i increase 5′ AMP-activated protein kinase and Sirtuin 1 which activates HIF-2 alpha the isoform responsible for the synthesis of EPO. Further studies are needed to highlight the contributions of these different mechanisms on anemia correction and whether mechanisms differed in diabetic and non-diabetic patients [40].

We also analyzed each SGLT2i by dose to determine whether there was a dose-dependent effect on hemoglobin and hematocrit levels. The change in hematocrit and hemoglobin levels differed according to the type of SGLT2i used. Our analysis showed that only dapagliflozin led to a significantly greater increase in hematocrit levels when administered in higher doses [10, 11, 23, 24]. However, there were no significant differences in blood parameters between the varying doses of canagliflozin, empagliflozin and ipragliflozin [9, 13, 28, 30].

It needs to be mentioned that the beneficial pleiotropic effects are valid for SGLT2i as a class effect. These effects (anti-inflammatory, anti-fibrotic, hemoglobin and hematocrit elevation) are independent of blood glucose lowering. It is probable that patients without diabetes and with kidney disease probably get a similar benefit from SGLT2 inhibition. Indeed it was already demonstrated that SGLT2i also improved outcomes in non-diabetic CKD patients [2].

Limitations

We acknowledge several limitations of our meta-analysis. The changes in hemoglobin and hematocrit levels after SGLT2i administration were not investigated as primary outcomes in the included studies. Furthermore, studies had not reported baseline and/or follow-up levels of erythropoietin, hepcidin and inflammatory markers following SGLT2i treatments. There was a wide heterogeneity between study populations and treatment protocols. Patients were not evaluated for different stages of kidney disease.

Conclusion

In conclusion, SGLT2i led to significant increases in hemoglobin and hematocrit levels when compared to placebo. These drugs can be used to prevent the adverse consequences of anemia and contribute to a better prognosis in patients with diabetes mellitus. Studies are needed to assess the impact of SGLT2i on anemia in patients with different stages of CKD and to further characterized the interaction of SGLT2i with iron availability. Furthermore, the potential relationship of changes in hemoglobin with outcomes should be explored in already available large clinical trials having clinical events as primary endpoints.

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Declarations

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