Sodium-glucose co-transporter 2 inhibitors and erythrocytosis: a review

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Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a class of anti-hyperglycaemic agents widely used in the treatment of type 2 diabetes mellitus (T2DM). They function by reducing renal glucose reabsorption and thereby promote urinary glucose excretion, resulting in improvement in glycaemic control. In large-scale clinical trials, SGLT2i have been shown to reduce cardiovascular mortality, non-fatal myocardial infarction and stroke significantly. In addition, clinical evidence suggests that they are renal protective as their use reduces the relative risk of end-stage renal disease and death from renal causes. These positive results have led to a rapid uptake of SGLT2i in clinical practice. Recently, clinical studies and case reports have suggested a link between SGLT2i therapy and erythrocytosis. The authors discuss possible mechanisms at cellular level that may cause erythrocytosis and explore its clinical relevance in people living with T2DM who are taking SGLT2i therapy.

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Introduction

SGLT2i, also known as gliflozins, are among the newer classes of oral anti-hyperglycaemic agents that are used for the treatment of type 2 diabetes mellitus (T2DM). In addition to improving glycaemic control in T2DM, the SGLT2i have demonstrated an array of beneficial effects, including but not limited to reduction in body weight, blood pressure, albuminuria, and renal and cardiovascular mortality.[1,2]

The National Institute for Health and Care Excellence (NICE) in the UK recommends that canagliflozin, dapagliflozin, empagliflozin and ertugliflozin may be used as first-line monotherapies for treating adults with T2DM in selected clinical circumstances.[3] In the real world, SGLT2i are commonly used as second- or third-line agents, mostly as an option for people who respond poorly to metformin monotherapy. They can be safely combined with various other glucose-lowering medications.[1] They are available as a single-drug product as well as in a fixed-dose combination with other diabetes medicines such as metformin.[4] Examples of commonly used medications which belong to the SGLT2i class are enumerated in Table 1.

Table 1 Commonly used SGLT2is in clinical practice

SGLT2i	EMA Approval	Dose (mg)
Dapagliflozin (Forxiga)	2012	5-10
Canagliflozin (Invokana)	2013	100-300
Empagliflozin (Jardiance)	2014	10-25
Ertugliflozin (Steglatro)	2018	5-15

EMA; European medicines agency

The benefits of SGLT2i use in clinical practice have been well established.[2,5] However, as with any medicinal product, there are certain adverse effects associated with its use which include dehydration, genitourinary infections, diabetic ketoacidosis, euglycaemic ketoacidosis and toe amputations.[6] Clinical reports and studies have pointed to an association of SGLT2i use with a rise in haematocrit (Hct) levels, which has become a topic of growing discussion and some concern among clinicians around the world. Clinical studies have found that an elevated Hct is significantly related to the incidence of cardiovascular disease (CVD), including myocardial infarction and stroke.[7]

In this article, the authors discuss the mechanism of action of SGLT2i and explore possible explanations of Hct and haemoglobin (Hb) elevation with their use, and ascertain whether this translates into an untoward outcome for the patients.

Methodology of search

We systematically searched PubMed, MEDLINE and Google Scholar for original articles, review articles, systematic reviews, randomized control trials (RCTs) and meta-analyses published in English from 01 January 2015 to 05 March 2022. We developed a search string of medical subject headings (MeSH) including the terms "sodium-glucose co-transporter 2 inhibitors", "effects of sodium-glucose co-transporter 2 inhibitors", "canagliflozin", "dapagliflozin", "ertugliflozin", "empagliflozin", "sodium-glucose co-transporter 2 inhibitors" and "haematocrit".

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Clinical studies

Several clinical studies have explored and described the relationship between SGLT2i and changes in haematological parameters.

In 2019, Maruyama *et al*. evaluated the erythropoietic effects of canagliflozin in nine people with T2DM with anaemia of chronic kidney disease over a period of 12 weeks. The results showed that the serum erythropoietin (EPO) concentration increased by 38% (p= 0.043) between baseline and 2 and 4 weeks, the reticulocyte count transiently increased at 2 weeks and there was a statistically significant rise in Hb (p=0.0049). The Hct levels also increased from week 2 until the end of the study period (from 37.1±2.3% at baseline to 40.4±3.2% at 12 weeks; p=0.002). The authors concluded that the effect on erythropoiesis appeared to be due to an EPO production-mediated mechanism which might be independent of glycaemic control.[8]

In 2020, Yamada *et al.* investigated the time-dependent alterations of various outcomes related to erythrocytes, erythropoiesis and clinical outcome in 89 people with T2DM treated with ipragliflozin for 16 weeks. Hct elevation was reported in 80% of the total cohort.[9]

In 2020, Mazer *et al*. studied the effect of empagliflozin on. erythropoietin levels, iron stores and red blood cell morphology in people with T2DM and coronary artery disease over a period of 6 months. The study concluded that empagliflozin treatment was associated with an early rise in plasma EPO levels, reduced ferritin and Hb concentration at 6 months in people with T2DM. At 6 months, the Hct increased by 2.34% (95% CI 1.1 to 3.57; p=<0.001).[10]

In 2020, Aberle *et al*. conducted a double-blinded, randomized, placebo-controlled trial extended over 104 weeks which studied the effect of variable doses of dapagliflozin on Hct, red blood cell count and reticulocytes in insulin-treated high-risk people with T2DM. For 48 weeks, patients were randomized to receive a placebo or dapagliflozin at a dose of 2.5, 5 or 10 mg daily. In addition, patients received their normal insulin dose and any oral hypoglycaemic agents. After 48 weeks, patients receiving 5 mg of dapagliflozin were switched to 10 mg. A short-term increase in reticulocytes at initiation of treatment was noted; however, the levels dropped to below baseline after 8 weeks. At 12 weeks, combined dapagliflozin and insulin treatment led to a dose-dependent rise in Hct compared to placebo and insulin. The mean change (± SD) in Hct (%) from baseline in the placebo group was −0.14 (± 1.88) vs dapagliflozin 2.5mg (1.57 ± 2.46) vs dapagliflozin 5/10mg (2.01 ± 2.17) vs dapagliflozin 10mg (2.13 ± 2.43). After this initial increase, the Hct levels remained stable until the end of the study.[11]

In 2021, Wang *et al*. conducted a systematic review and meta-analysis of 40 RCTs (21,050 participants) to evaluate the effects of SGLT2i on Hct in people with T2DM. The results suggested that there was a significant increase in Hct in people treated with SGLT2i compared to placebo (weighted mean difference [WMD] 2.67%, 95% CI 2.53 to 2.82; p=<0.001). This appeared to be a class effect, with empagliflozin causing the largest increase in Hct levels followed by canagliflozin, ertugliflozin, dapagliflozin and ipragliflozin. Moreover, the increase in Hct levels was more pronounced at higher doses of the medication studied.[12]

In 2021, Tian *et al*. conducted a meta-analysis of 78 clinical studies on the effects of SGLT2i on Hct and Hb levels and the associated cardiorenal benefits in people with T2DM. The results suggested that, compared to controls, the SGLT2i significantly increase the Hct (the total WMD 2.27% [95% CI 2.08 to 2.47], p= 0.000) and Hb levels (the pooled WMD of the effect of SGLT2 inhibitors on haemoglobin was 6.20 g/L [95% CI 5.68, 6.73], p= 0.000). A dose-dependent relationship between SGLT2i and Hct/Hb rise could be established for dapagliflozin but not for other SGLT2i. Moreover, this meta-analysis suggested that the effect could be sustained or even slightly increased with long-term therapy. Tian *et al*. identified that changes in Hct and Hb could be used as surrogate markers for the improvement in renal metabolic stress, and were important mediators involved in cardiorenal protection.[13]

Mechanism of action of SGLT2i

Sodium-glucose co-transporters (SGLTs) regulate sodium and glucose transport across the cell membranes. SGLT1 and SGLT2 contribute to renal tubular glucose absorption, preventing glycosuria. A total of 6 SGLT isoforms have been identified in human beings; however, only SGLT1 and SGLT2 inhibition have translated into pharmacotherapy in T2DM so far. The SGLT2 is a low-affinity and high-capacity transporter responsible for >90% glucose reabsorption from the S1 and S2 segments of the proximal convoluted tubule (PCT) in the nephrons. Inhibition of SGLT2 leads to glucosuria and improved glycaemia in people with T2DM. SGLT1, on the other hand, is a high-affinity but low-capacity transporter which mediates the absorption of glucose mainly in the small intestine but also accounts for the reabsorption of approximately 3% of the filtered glucose from the S3 segment of the PCT.[6,14]

Erythrocytosis, polycythaemia and haematocrit (Hct)

The terms erythrocytosis and polycythaemia are sometimes used interchangeably but there is a slight difference in these entities in that erythrocytosis is an increase in RBCs relative to blood volume whereas polycythaemia is an increase in both RBC concentration and Hb. Hct can be defined as the volume percentage of red blood cells (RBCs) in total blood.[15]

A high Hct level has been linked to an increased risk of cardiovascular disease; however, the relationship between a low Hct level and cardiovascular disease is controversial. It is well established that the Hct and Hb levels are amongst the major factors affecting blood viscosity and dynamics of tissue oxygen delivery. It is thought that variations in blood viscosity and oxygen delivery alter vascular function and structure. In a recent study, Kishimoto *et al*. assessed the relationship of Hct, Hb and RBCs with vascular structure and function.[16] They demonstrated that abnormally high and low levels of Hct, Hb and RBCs were associated with vascular smooth muscle dysfunction whereas low Hct was also shown to be associated with abnormal vascular structure.

Table 2 shows the reference ranges of Hct in males and females. However, these vary based on the methodology used and the normal ranges should be validated by the reporting laboratories.[17]

Table 2 Reference ranges for haematocrit (%)

Males	40 - 54
Females	36 - 46

SGLT2i therapy and its relationship with erythrocytosis, erythropoietin (EPO) and haematocrit (Hct)

Erythrocytosis can be congenital or acquired. Both entities can be due to an intrinsic defect in RBCs (primary) or due to a cause extrinsic to RBCs (secondary). Erythrocytosis is mostly acquired and is seen in conditions prone to result in hypoxaemia (smoking, sleep apnoea, living in high altitude areas, carbon monoxide poisoning) or overproduction of EPO (cerebellar haemangioblastoma, parathyroid carcinoma, meningioma). It is also a common side effect of various drug therapies, including but not limited to diuretics, testosterone and recombinant human EPO. Rarely, erythrocytosis has a genetic basis, acquired in polycythaemia vera (PCV) due to a mutation in the Janus tyrosine kinase 2 (JAK2) gene which results in an overproduction of RBCs from the bone marrow.[18]

SGLT2i therapy promotes glycosuria. This results in osmotic diuresis which increases the Hct by up to 4% compared to placebo, an effect that is consistent with all medicinal products within this class.[19] The Hct rises soon after initiation of therapy and tends to remain elevated for as long as the treatment with SGLT2i continues.[20] One possible explanation is that the diuretic effect of SGLT2i increases the urine volume, causing haemoconcentration and a resultant rise in Hct. However, the increase in urine volume after SGLT2i initiation peaks at 24 hours before returning to baseline after 1 week. This decrease in osmotic diuresis can be explained by the improvement of glycaemic control with SGLT2i therapy. On the other hand, the Hct continues to rise for up to 8 weeks, which suggests that this pattern of Hct rise is independent of haemoconcentration due to osmotic diuresis. The delay in reaching the peak Hct (8 weeks) can be attributed to the time taken by the physiological triggers enacted by SGLT2i therapy in inducing erythropoiesis, which is dependent on many factors including the RBC life span.[19]

In clinical practice, an elevated Hct is seen as an indication of haemoconcentration secondary to the diuretic effect exerted by SGLT2i. Although the risk of cerebrovascular accidents (CVA) is not increased, clinicians may be inclined to discontinue SGLT2i use in people with excessive Hct elevations, potentially depriving them of several beneficial effects from this medication.[20-22]

Another explanation could be rising erythropoietin (EPO) levels that have been reported with the initiation of dapagliflozin and level out at 4 weeks. The rise in EPO may result in elevation of reticulocyte count followed by Hb and Hct.[19,23] While this may be a byproduct of haemoconcentration as well, there are suggestions that SGLT2i use can stimulate erythropoiesis by the following mechanisms:[19,20,24,25]

- Sodium levels rise at the distal renal tubules, which results in an increase in the afferent arteriolar tone with a consequent reduction in afferent renal blood flow, glomerular filtration rate and tissue oxygen delivery
- When cells in the proximal renal tubule are relieved from excess glucose absorption, cortical oxidative stress is reduced which facilitates tubulointerstitial recovery and restores EPO production
- SGLT2i therapy results in the elevation of β-hydroxybutyrate (β-OHB), which is a ketone body and a specific endogenous inhibitor of class I histone deacetylases. Elevation of intrinsic β-OHB promotes acetylation of H3K9 and H3K14 (renal histones) which induces genes that resist oxidative stress in the tubulointerstitial region. Reduction in the oxidative stress in the renal cortex via the described mechanism is thought to facilitate the recovery of EPO production

Clinical relevance

Elevated Hct is significantly related to the incidence of CVD, including myocardial and cerebral infarction.[7] However, there is also evidence to suggest that both elevated and reduced Hct levels can pose a cardiovascular (CV) risk, though the influence on CVD subtypes is variable.[26]

In people with T2DM taking SGLT2i, though an elevation of Hct is well documented these medications have been shown to provide cardiorenal protection in this cohort and this may be one of the mechanisms through which they exert this protection.[13]

In patients with T2DM, the serum EPO is low in the presence of a normal kidney function which falls further as the HbA_{1c} level increases.[27] In a hyperglycaemic milieu, excessive glucose resorption results in metabolic stress which causes a hypoxic environment in the PCT. Consequently, the erythropoietin-producing fibroblasts are converted to myofibroblasts, which is one explanation for lower EPO levels in people with T2DM. The metabolic stress in the PCT is mitigated by the SGLT2i, which reinstates the myofibroblasts. These cells in turn enhance haematopoiesis and elevate the Hct. In addition, by counteracting diabetes-induced increased glucose and sodium reabsorption from the PCT, sodium and fluid delivery are increased distally to the macula densa. This lowers the glomerular filtration rate (GFR) through the physiology of tubulo-glomerular feedback (afferent arteriole constriction, potential dilation of the efferent arteriole resulting in reduced glomerular capillary pressure) and increase in hydrostatic pressure in the Bowman's capsule.[28] In this way, SGLT2i suppress not only the development of nephropathy but also the progression of chronic kidney disease in T2DM.

Numerous mechanisms have been described to explain the cardioprotective effects of SGLT2i, which include but are not limited to the reduction of blood pressure, improved cardiac energy metabolism, increased diuresis and natriuresis, reduction in inflammation, prevention of ischaemia/reperfusion injury and inhibition of the sympathetic nervous system.[29] Moreover, in people with heart failure, the sodium/hydrogen exchanger (Na^+/H^+) is increased leading to Na^+ and Ca^{2+} overload.[30] SGLT2i-mediated inhibition of the sodium/hydrogen exchanger (Na^+/H^+) has been proposed as one of the mechanisms via which they exert their cardioprotective effect.[29] An elevation of the Hct is linked to the alleviation of sympathetic overactivity, which leads to a reduction in hospitalization with heart failure and cardiovascular mortality in people with T2DM

taking SGLT2i.[11,19] These metabolic and physiological changes explain how the rise in Hct and Hb in this cohort of patients confers a cardiorenal benefit.

Das *et al*. reported a case of a 51-year-old male with T2DM treated with canagliflozin 100 mg OD. Following 6 months of treatment he presented with an asymptomatic elevation of Hb (16.9 g/dL) and Hct (55%). Further investigations revealed JAK2V617F positivity. Discontinuation of canagliflozin led to a significant improvement in the haematological profile. In this case, PCV was unmasked by SGLT2i use.[31]

Discussion

Evidence from large-scale clinical trials and clinician experiences have without doubt proven that benefits from SGLT2i therapy far outweigh any risks posed from their use. For instance, not only did empagliflozin (EMPA-REG) reduce the 3-point major adverse cardiac events (cardiovascular death, non-fatal myocardial infarction and stroke) but it was also shown to reduce cardiovascular death (by 38%), hospitalization with heart failure (by 35%) and all-cause mortality (by 32%).[5,32,33] In the CREDENCE trial, people with albuminuric chronic kidney disease (CKD) and T2DM received canagliflozin vs placebo. At a median follow-up of 2.62 years, the relative risk of a doubling of the creatinine level or death from renal causes was reduced by 34%, whereas the relative risk of end-stage kidney disease was reduced by 32%.[2] These remarkable results have led to a rapid uptake of this therapeutic class in the management of T2DM. Nonetheless, the treating clinicians should be aware of possible adverse effects and counsel their patients in taking appropriate preventive measures.

From the studies discussed in this article, it is evident that SGLT2i therapy in people with T2DM results in an elevation of Hct and Hb, and in this setting this rise confers cardiorenal protection. Further exploration into the mechanisms leading to erythrocytosis with SGLT2i is required.

The authors are aware of only five cases of severe erythrocytosis with SGLT2i reported in literature thus far.[34-36] Of these cases two were also on testosterone replacement therapy, which is an established cause of secondary erythrocytosis,[36] and in one instance a diagnosis of PCV was uncovered.[31] Due to the widespread use of SGLT2i in clinical practice, the incidence of severe erythrocytosis is likely to rise, which may be of concern to some healthcare professionals. However, the authors seek to reiterate that there have been no cases of symptomatic increase in Hct with SGLT2i therapy and no causal links have been made with PCV. Furthermore, where severe erythrocytosis has been picked up in the context of SGLT2i therapy, other established causes of secondary erythrocytosis such as concomitant testosterone administration have been found which can also explain the rise in Hct/Hb.

Evidence suggests that the Hct rises soon after initiation of SGLT2i therapy and remains elevated for the duration of treatment.[20,22] Authors advise against routine Hct monitoring in this cohort but if there are clinical concerns pointing to a diagnosis of primary or secondary polycythaemia, clinicians should take a stepwise approach towards investigation to facilitate determination of the cause, as suggested by Mithoowani *et al*.[37]

Key messages

- Considering the available clinical evidence, the benefits of SGLT2i therapy outweigh any risks posed by their use.
- SGLT2i therapy can increase haemoglobin and haematocrit levels; however, this has been shown to be beneficial for cardio-renal health.
- Authors do not recommend routine haemoglobin or haematocrit monitoring in people on SGLT2i therapy.

The SGLT2i have been in clinical use for more than 10 years and are an important class of anti-hyperglycaemic medication owing to their effectiveness in improving glycaemic control and providing significant cardiorenal protection. In addition to their use in T2DM, SGLT2i are being used in the treatment of heart failure in people without T2DM as they have been shown to improve cardiovascular outcomes in this cohort.[38] Furthermore, they have been found to be effective in preservation of renal function, therefore are being used to treat people with CKD.[39] The confidence of clinicians when it comes to prescribing SGLT2i is growing, with substantial therapy initiations now occurring in the community and non-diabetes clinics (cardiology and nephrology). To maintain this confidence, it is essential to address any concerns that come to light in relation to SGLT2i. The authors suggest that all patients receiving SGLT2i therapy be adequately counselled regarding risk of dehydration, possibility of genitourinary infections and sick-day rules. Clinicians must emphasize the importance of staying well hydrated and observing good personal hygiene to minimize the aforementioned risks.[6] As described in this article, it is prudent to take a balanced approach in risk mitigation, avoidance of over-investigation and unnecessary specialty referrals when dealing with a rising Hct in the context of SGLT2i therapy. This will ensure that SGLT2i therapy is only discontinued when it is clinically indicated, and people are not unnecessarily deprived of the extensive short- and long-term benefits they stand to gain from their use.

Conclusion

The SGLT2i are a potent class of anti-diabetic medication that not only improve glycaemia, but also offer cardiorenal protection when used for the treatment of T2DM. They can result in an increase in Hct and Hb, which has been shown to have a beneficial effect on cardiac and renal health in this cohort; however, this remains to be fully established. Occasionally, they may cause erythrocytosis but there is no evidence of adverse clinical outcomes in these cases and no causal link with PCV has been established. Therefore, the authors advise against routine Hct monitoring in SGLT2i-treated people with T2DM. When there is evidence of persistent erythrocytosis, a stepwise approach in investigation and management is prudent to delineate the cause.

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