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Review Article:

An Overview of the Effects of Sodium-Glucose Co-Transporter-2 Inhibitors on Hematological Parameters in Diabetic Patients

Ghada M. Ahmed[1], Mohammed N. Abed[2], Fawaz A. Alassaf[3,4]

[1] *Nineveh health directorate, Mosul, Nineveh province, Iraq.*
[2] *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*
[3] *Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq.*
[4] *College of Medicine, University of Warith Al-Anbiyaa, Karbala, Iraq.*

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Abstract

Background: Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2-IS) have been shown to increase hemoglobin (Hb) levels, hematocrit, and erythrocyte count. It has also been found that these agents can potentially reduce the risk of anemia and minimize the need for erythropoiesis stimulating agents (ESA) and other treatments in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). However the precise mechanism for such an effect is still conflicting. **Aim:** We aimed at providing an overview of the effects of SGLT2-IS on hematological parameters, specifically focusing on their potential to improve anemia and erythropoiesis in patients with diabetes mellitus (DM). Additionally the proposed mechanisms by which SGLT2-IS may improve Hb levels besides their clinical importance and future directions will also be highlighted. **Results:** Based on the obtained data from latest literatures, SGLT2-IS may improve the status of anemia and other linked abnormalities via their mild diuretic potential, effects on erythropoietin (EPO) production, and possible increase in renal oxygen delivery. **Conclusion:** SGLT2-IS may have a promising role in improving multiple aspects of blood, circulatory and renal systems health in patients with DM, beyond their primary glucose-lowering role.

1. Introduction

The Diabetic people are prone to anemia and other blood disorders. Diabetes duration and severity, renal diseases, inflammation, hyperglycemia and poor nutrition are all associated risk factors for developing anemia in diabetic individuals (1). Moreover, several anti-diabetic drugs, while they are useful in regulating blood sugar levels and lowering the risk of complications, may raise the risk of anemia (2,3). During the last decades, there has been a considerable shift toward the development of new treatment alternatives, including newer oral anti-diabetic drugs capable of controlling glucose levels and preventing diabetic complications such as anemia (4,5). SGLT2-IS are a new category of anti-diabetic agents that have been shown to have various favourable impacts on hematological and biochemical parameters by targeting different routes involved in regulation of glucose and erythropoiesis. Enhancement of EPO release from the kidney, red blood cells synthesis and reduction of glucose level, with significant impact on the metabolism of lipids via reducing subcutaneous and visceral fat and lipid accumulation are examples of beneficial SGLT2-IS effects (6,7). Moreover, SGLT2-IS have the potential to lower the risk of cardiovascular (CV) mortality rates, thereby improving the quality of life in patients with T2D. However, they can have negative effects and may not be appropriate for all patients as bladder and breast cancer risk is still a concern for SGLT2-IS safety (8). The present review aimed at highlighting the impact of SGLT2-IS on hematological parameters, particularly anemia, in T2D patients, as well as

*Corresponding author: Mohammed N. Abed, Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.

E-mail: m.n.abed@uomosul.edu.iq

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to identify the potential mechanisms and modifiers involved in such an effect. Besides, the potential recommendations for clinical practice regarding how to screen hematological parameters in subjects receiving these medications will be provided along with future directions for their use in diabetic and non-diabetic individuals. Cochrane Library, Google Scholar and PubMed were searched using key words relevant to the main topic of the article to identify and analyse the publications that meet our criteria up to the date of drafting this review.

1.1 Sodium Glucose Co-Transporter Inhibition and glycemic control

Normally, all of the filtered glucose is re-absorbed in the tubules of the kidney, hence no glucose is found in the urine (9). SGLT2 presents in the early S1 segment of the proximal convoluted tubule (PCT) help to reabsorb about 80% to 90% of the filtered glucose, whereas SGLT1s in the S2/S3 segments are responsible for reabsorption of the remaining 10% to 20% of glucose. Accordingly, any unabsorbed glucose by SGLT2 is thereby reabsorbed by SGLT1 in far distal convoluted segments (10). SGLT2s are also found in the cerebellum and pancreatic α-cells, whereas SGLT1s are found in the intestine, skeletal muscles, kidneys, lungs and heart (11). SGLT2-IS block the sodium/glucose transporter in the renal PCT, causing urine glucose loss and reducing blood glucose levels (12). This modern form of ancient medicine has a long and storied history, the first substance in this class, "phlorizin," or "O glucoside phlorizin dihydrochalcones", was isolated from the apple tree bark in 1835 by French chemists (13). Joseph Vas Mering, a renowned diabetologist, later described the medicinal role of SGLT inhibitor consumption as causing glycosuria in 1886 (14). Phlorizin was discovered to help diabetic animals maintain better glycemic control (15). The main problem that prevented its usage in humans was the dosage, since most phlorizin is transformed into an intermediate before it can be used. This necessitates an increase in dose to obtain the required hypoglycemic effect (16). As a beta glycoside, phlorizin was poorly tolerated throughout the GIT and caused a number of unpleasant adverse medication events. Accordingly, phlorizin was never developed into a powerful oral anti-diabetic therapy (17).

However, researches have been trialled to adopt the basic structure of phlorizin to introduce new agents with similar activity and minimal adverse effects. Such novel diabetes medication to be legally approved, they must demonstrate successful glycemic control results when analysing the glycated Hb (HbA1c), fasting serum glucose, and postprandial blood glucose readings (18,19). The obtained SGLT inhibitors constituted a new family of medications that were created by extrapolating this action and have finished a number of phase 3-double blind, placebo controlled studies that focus at the glycemic impact when administered to either treatment-naive individuals or those receiving insulin, biguanides, sulfonylureas, thiazolidinediones, dipeptidyl deptidase 4 inhibitors or glucagon-like peptide 1 receptor agonists (GLP1 agonists) as monotherapy (17). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have authorized four oral medications of SGLT2-IS for the management of T2D, including: Dapagliflozin (Dapag), Canagliflozin (Canag), Empagliflozin (Empag), and Ertugliflozin (Ertug) (20). Dapag, which was introduced in 2008, has a potency for SGLT2 1200 times more than that for SGLT1 (21). Another phlorizin derivative called Canag inhibits SGLT2 400 times more potently than it does on SGLT1 (22). The third compound in this group was Empag, which among the commercially available SGLT2-IS, has the maximum selectivity for SGLT2 versus SGLT1 (about 2700 times) (23). Ertug, the fourth developed phlorizin derivative, is 2200 times more specific for SGLT2 than SGLT1 (11). SGLT2 Inhibitors' impact on blood glucose concentrations is dose-dependent and equivalent to that of other old anti-diabetic medications. Alongside enhancing glycemic status via lowering HbA1c levels, these agents protect against diabetic nephropathy, CVD and weight. The proposed mechanism for these activities may be via lowering high glucose levels as well as obesity's impacts on kidney inflammation, apoptosis, fibrosis, endoplasmic-reticulum stress and lipid accumulation, in addition to their benefits in reducing reactive oxygen species, epithelial to mesenchymal transition, as well as RECK suppression induced by elevated glucose (24,25). Additionally, the most common adverse effect of most oral anti-diabetic medications, which is hypoglycemia, is not experienced by individuals using SGLT2-IS. This may be attributable to SGLT2 inhibition rather than SGLT1 inhibition, as SGLT1 maintains residual reabsorption of glucose in the PCT, which is sufficient to keep the blood glucose amount close to normal. Accordingly, in the absence of other co-treatments that might potentially cause hypoglycemia, SGLT2-IS do not cause it (26).

1.2 Sodium Glucose Co-Transporter inhibition and erythropoiesis

Anemia is a challenging complication in diabetic patients with CKD, as it worsens their prognosis (27). Observational studies indicate that anemia is a significant independent predictor of the progression of CV morbidity and mortality (28,29). Previous trials involving ESA have shown that increasing Hb concentrations did not reduce the risk of adverse CV or kidney outcomes in patients with CKD, with or without T2D (30–32). Therefore, there is a pressing need for new treatment options to manage anemia in patients with T2D and kidney problems. SGLT2-IS are known to inhibit the reabsorption of both glucose and sodium in the proximal tubule, resulting in a mild diuretic effect (33). This effect has been linked to a reduction in plasma volume, as well as improvements in blood pressure, body weight, and an increase in haematocrit. The elevation in haematocrit is commonly attributed to haemo-concentration (34). However, SGLT2-IS may also have a temporary impact on EPO levels and the reticulocyte count (by lessening the stress on the PCT and enhancing tubule-interstitial hypoxia leading to enabling kidney tissue to start producing EPO again (35)), which in turn, increase the haematocrit and Hb in a manner that is not dependent on volume. These erythropoietic effects suggest that SGLT2-IS could potentially decrease the incidence of anemia (36,37). In a post-hoc analysis of the CREDENCE trial, Oshima et al. observed that the proportion of patients with anemia events was significantly lower in the Canag group than in the placebo group during a follow-up of more than 2 years. The patients in the Canag group also experienced an increase in Hb, haematocrit, and erythrocyte count compared to those in the placebo group. The effects of Canag on Hb were proportionally greater than its effects on serum albumin, suggesting that direct effects on erythropoiesis contributed to the observed increases in Hb concentrations (38). In addition to improving kidney and CV outcomes, the available evidence suggests that Canag may also reduce the risk of anemia and decrease the need for ESAs and other anemia treatments in patients with T2D and CKD (38).

The above findings has been supported by a study published in the Journal of Diabetes and its Complications in 2020 by Stefánsson and colleagues, who demonstrated that Dapag treatment led to an increase in Hb levels among patients with T2DM and CKD, where the researchers suggested that this effect may be due to an increase in EPO level (39). More recently, Murashima et al. reported that the use of SGLT2-IS was associated with higher Hb levels among patients with advanced kidney diseases, and that the use of these inhibitors was linked to a lower incidence of anemia in real clinical settings among patients with DM, active malignancy, or acute illness (40). Another suggested mechanism by which SGLT2-IS may enhance Hb levels and other hematological parameters in diabetic patients is by boosting renal oxygen delivery. Although this mechanism has primarily been observed in diabetic patients with normal kidney function, SGLT2 inhibition reduces glucose load in the kidney, which enhances renal oxygen consumption (41). As a result, the improvement of renal tubular interstitial hypoxia occurs by elevating renal oxygen delivery, accompanied by fibroblast restoration to produce EPO, leading to an increase in Hb levels (42). In 2019, a study published in Diabetes Technology and Therapeutics by Maruyama et al, investigated patients with diabetes receiving 100 mg of Canag as a single daily dose throughout three months. Prior to enrolment, the patients were administered angiotensin receptor blockers and conventional hypoglycemic agents at set dosages for two months; these medications were maintained throughout the course of the study. Endpoints included variations in erythropoiesis markers from baseline to three months. The study reported that treatment with Canag improved anemia and EPO levels in patients with T2D and CKD, highlighting the effects of anemia and hypoxia on the ability of SGLT2 inhibitors to induce erythropoiesis (43). Additionally, another study found that SGLT2 inhibition temporarily boosts EPO levels, and the rise in hematocrit associated with SGLT2 inhibition may be attributed to the normalization of renal cortical oxygenation, leading to the normalization of EPO-producing cells (44).

It has been reported that SGLT2-IS can upregulate the AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), while inhibiting the hypoxia-inducible factor (HIF-1α) and activating HIF-2α (45,46). This suggests that the increased production of EPO and correction of anemia with these drugs may be mediated through HIF-2α, which is responsible for EPO synthesis as illustrated in **Figure 1**. Additionally, SGLT2-IS inhibit hepcidin, which could result in increased iron bioavailability and utilization, leading to increased RBC production. Based on these effects on erythropoiesis, it is possible that SGLT2-IS could lower the incidence of anemia (47–49).

The effect of SGLT2-IS on hematological parameters may also be attributed to a reduction in oxidative stress. Animal models have shown that these inhibitors can decrease oxidative stress, which is known to inhibit EPO production (50). This mechanism could potentially regulate other hematological parameters such as white blood cells and platelets, resulting in a significant reduction in CV risk for patients with T2D (50,51). To evaluate the effect of Empag on systemic inflammation and its potential antioxidant properties, an observational prospective follow-up study by Iannantuoni and colleagues in 2019 was conducted on patients with T2D who received a daily dose of 10 mg of Empag for 24 weeks. The study showed that, in addition to reducing body weight, glucose and HbA1c levels, Empag treatment reduced superoxide production in leukocytes of diabetic patients and increased glutathione content. Furthermore, Empag treatment enhanced the expression of glutathione s-reductase and catalase in leukocytes and increased serum levels of IL-10, while reducing hs-CRP and myeloperoxidase levels at the end of the study (52). These findings indicate that Empag treatment has antioxidant and anti-inflammatory properties in humans, which may contribute to its beneficial CV effects (52). Another study conducted by Pignatelli et al in 2022 on T2D patients, whom were already undergoing metformin therapy to evaluate the potential cardioprotective effects of GLP1 receptor agonists and gliflozins. The study revealed that gliflozins treatment decreased the levels of sNOX2-dp, H_2O_2 production, Thromboxane B2, sP-selectin, and sCD40L, as well as thrombus formation. This effect was accompanied by an increase in antioxidant power, indicating that gliflozins could protect against atherothrombotic-related complications induced by platelet activation and oxidative stress (53). In addition, an in vitro study conducted by Lescano and colleagues in 2020 on stimulated platelets treated with gliflozins demonstrated a reduction in oxidative stress, platelet activation, and thrombus growth, further supporting the potential cardioprotective effects of gliflozins (54).

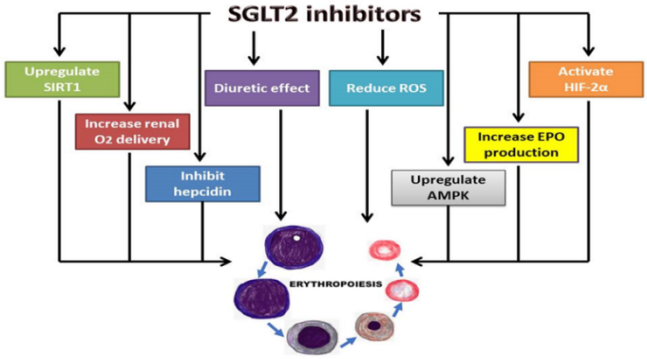

Figure 1. Outlined mechanism of SGLT2 inhibition and induction of erythropoiesis

1.3 Clinical significance of SGLT2-IS

The hematological improvements linked to SGLT2 inhibitor usage are essential because they imply that these medications may have advantages for the blood and circulatory system in addition to their primary objective to reduce blood glucose levels in T2D patients (55). Anemia, which is common among people with diabetes and can increase the chances of CVD hospitalization and mortality, is related to low levels of RBCs. Accordingly, the hematological enhancements that occur as a result of using SGLT2-IS can have a significant impact on clinical outcomes because they may lower the likelihood of developing CVD, a complication that is often associated with diabetes (56,57). Moreover, diabetic patients who suffer from hypertension may benefit from SGLT2-IS, as studies have shown that drugs in this class have the ability to lower blood pressure and potentially protect the heart. Additionally, SGLT2-IS have been found to decrease oxidative stress and hinder hepcidin, which could lead to increased availability and utilization of iron, resulting in the production of more RBCs. This could offer an alternative explanation for how SGLT2-IS may decrease the occurrence of anemia and other blood-related disorders (58–61).

Besides their positive effects on RBC production and CV health, SGLT2-IS have been recently observed to have potential impacts on other aspects of blood physiology. For instance, they have been found to lower the count of white blood cells, which suggests a possible anti-inflammatory effect (62). Additionally, SGLT2-IS have been shown to decrease the formation of blood clots, activation of platelets, and markers of blood clotting, which could lower the likelihood of CV events in diabetic patients (54). Nonetheless, it is important to monitor platelet count periodically for patients using SGLT2-IS, especially those taking anticoagulants or antiplatelet agents, as there have been reported cases of thrombocytopenia and bleeding (63). Similarly, monitoring the white blood cell count is also necessary to address any potential increase in the risk of infections (64). Moreover, the beneficial effects of SGLT2-IS on the heart may extend beyond what was previously mentioned. Various studies have demonstrated that these drugs can lead to slight weight loss in some patients, possibly due to a decreased appetite or loss of calories through urine (65). A meta-analysis of randomized-controlled trials performed by Cho et al in 2021 to assess the effectiveness of SGLT2-IS in treating obesity in non-diabetic obese or overweight people established a significant weight lowering effect of SGLT2-IS in obese individuals without DM. This is mostly caused by a reduction in body fat and may be linked to a change in adipokines that regulate body weight (66).

SGLT2-IS have demonstrated the ability to decrease the risk of kidney disease progression, a prevalent complication of diabetes. One possible way that SGLT2-IS exert their protective effects on the kidneys is by improving hematological parameters (67). Chronic kidney disease is a common complication of diabetes that is linked to a higher likelihood of anemia, bleeding disorders, and CV events (68). Clinical studies (such as DAPA-CKD trial of Dapag in patients with CKD with or without T2DM and the CREDENCE trial, which examined Canag in patients with CKD and T2D (69,70)) have shown that SGLT2-IS can improve kidney function, decrease albuminuria, and slow the progression of kidney disease in patients with T2D. This may be beneficial in preventing or delaying the onset of hematological complications associated with CKD (71–73).

Conversely, it is important to recognize that SGLT2-IS could potentially increase the likelihood of developing genital and urinary tract infections, which may result in complications like pyelonephritis (74). SGLT2-IS were predicted to contribute to glucosuria, as a result of their mode of action, causing propensity for commensal microbial proliferation, and predispose to urethral infections (75). In certain situations, these infections could also cause hematuria, which can influence the accuracy of Hb measurements. Therefore, it is advised to monitor renal function prior to and during treatment (76). Furthermore, while treatment with SGLT2-IS can increase Hb and hematocrit levels, it is possible that this could lead to elevated blood viscosity and potentially result in thromboembolic events and venous occlusion. As a result, it is suggested to regularly monitor Hb and hematocrit levels at the start of treatment and throughout the course of treatment (77). This is especially important due to recent concerns that have arisen from Lee et al study, which indicated that SGLT2-IS had an adverse effect on blood vassels in patients with T2D and may result in retinal vein occlusion (78). White blood cell count should also be monitored as SGLT2-IS have been shown to reduce white blood cell counts, which is linked to their anti-inflammatory properties. However, this reduction could potentially increase the risk of infections. Therefore, it is recommended to monitor white blood cell counts before treatment and regularly throughout the treatment process (79).

2. Future aspects

Current clinical trials are expected to provide more insights into the potential uses of SGLT2-IS. While some studies have shown promising results when using these drugs as adjunct therapy to insulin in patients with T1D, it is recommended to be used with caution in this population (80). Clinical trials with Dapag, Empag, and Canag have shown reductions in HbA1c and weight without increased hypoglycemia events, but a higher incidence of diabetic ketoacidosis was observed in the SGLT2-IS group (81,82). None of these drugs have been approved by the FDA for use in T1D (83). To expand the use of SGLT2-IS in T1D, on-going clinical trials are evaluating their adjunctive use with closed-loop insulin pumps and combination therapy with GLP1 agonists (84). One of the drugs being studied for T1 and T2D is Sotagliflozin (Sotag), which is a dual inhibitor of SGLT1 and SGLT2. SGLT1 is located in the proximal intestine, and inhibiting it reduces glucose absorption and delays postprandial hyperglycemia (85). A phase 3 clinical trial tested the efficacy and safety of Sotag as an add-on therapy to insulin in patients with T1D, and although the drug was effective in improving glycemic control, the rate of diabetic ketoacidosis was higher compared with placebo. As a result, the FDA rejected Sotag as adjunct therapy for T1D. However, there is a clinical trial aimed at studying the efficacy of Sotag in T2D and its results are yet to be published. On the other hand, Sotag (200 or 400 mg) has been authorized by the European Commission as an oral treatment for patients with body mass index of at least 27 kg/m^2, where healthy participants handled the drug well when administered as a single daily dose (86).

In conclusion, the use of SGLT2-IS can help in reducing the risk of CV and kidney disease complications in diabetic patients by improving hematological parameters. Additionally, SGLT2- IS may have a positive effect on Hb levels in certain populations, but changes in Hb levels and other potential side effects should be monitored. These drugs have the potential to improve multiple aspects of

blood and circulatory system health in diabetic patients, beyond their primary glucose-lowering effects, and evaluating hematological outcomes is important when considering the benefits and risks of SGLT2 inhibitor therapy.

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4. Conflict Of Interest

There is no conflict of interest.

5. Reference

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نظرة عامة على تأثيرات مثبطات نواقل الصوديوم-الجلوكوز-2 على معالم الدم لدى مرضى السكري

ثبت أن مثبطات نواقل الصوديوم- الجلوكوز-2 تزيد من مستويات الهيموجلوبين، والهيماتوكريت، وعدد كرات الدم الحمراء، مما قد يقلل من خطر الإصابة بفقر الدم ويقلل من الحاجة إلى العوامل التى تحفز تكون الكريات الحمر والعلاجات الأخرى فى مرضى السكرى من النوع الثانى وأمراض الكلى المزمنة. لكن الآلية الدقيقة لمثل هذا التأثير لا تزال متضاربة. لقد هدفنا إلى تقديم نظرة عامة عن تأثيرات مثبطات نواقل الصوديوم- الجلوكوز-2 على معالم أمراض الدم ، مع التركيز بشكل خاص على قدرتها على تحسين فقر الدم وتكوين الكريات الحمر فى مرضى السكرى. بالإضافة إلى الآليات المقترحة التى من خلالها يمكن لـهذه الادوية تحسين مستويات الهيموغلوبين إلى جانب أهميتها السريرية وسيتم أيضًا تسليط الضوء على الاتجاهات المستقبلية. كشف تحليل البيانات التى تم الحصول عليها أن مثبطات نواقل الصوديوم- الجلوكوز-2 قد تحسن حالة فقر الدم والتشوهات الأخرى المرتبطة من خلال إمكاناتها كمدررات بول خفيفة ، والتأثيرات على إنتاج الإريثروبويتين، والزيادة المحتملة فى توصيل الأكسجين الكلوى. بشكل عام ، قد يكون لمثبطات نواقل الصوديوم- الجلوكوز-2 دور واعد فى تحسين جوانب متعددة من صحة الدم والدورة الدموية والجهاز الكلوى لدى مرضى السكرى، بما يتجاوز دورهم الأساسى فى خفض الجلوكوز.

الكلمات المفتاحية: مثبطات نواقل الصوديوم- الجلوكوز-2، فقر الدم، الارثروبويتين