Risk of Erythrocytosis During Concomitant Testosterone and SGLT2-Inhibitor Treatment: A Warning From Two Clinical Cases

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Context: Erythrocytosis is one of the most common side effects occurring during testosterone replacement therapy (TRT) in male hypogonadism. It is well known that all testosterone formulations may cause Hb and hematocrit increase, especially with short-acting injectable formulations. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a new class of glucose-lowering agents that reduce hyperglycemia in patients with type 2 diabetes mellitus (T2DM) by inhibition of renal glucose reabsorption, leading to increased urinary glucose excretion. The co-occurrence of T2DM and hypogonadism is known to be increasingly frequent. However, to date, no adverse events with the concomitant use of TRT and SGLT2is are reported.

Case Description: We report two cases of erythrocytosis during testosterone treatment and SGLT2i in patients with hypogonadism and T2DM.

Conclusion: Considering that hypogonadism and T2DM are frequently associated, clinicians should carefully monitor the risk of occurrence of erythrocytosis when prescribing TRT and SGLT2i together. (***J Clin Endocrinol Metab*** **104: 819–822, 2019)**

R.C. is a retired 68-year-old nonsmoking man with a 10-year history of type 2 diabetes mellitus (T2DM) treated with metformin 2 g daily, glimepiride 3 mg daily, and exenatide long-acting release 2 mg once weekly. Referred by his family physician to the diabetes specialty clinic, R.C. presented with nonoptimal glycemic control and a stable class I obesity with no coexisting obstructive sleep apnea syndrome.

He also suffered from noncomplicated arterial hypertension and hypercholesterolemia treated with daily amlodipine 5 mg, telmisartan 160 mg, hydrochlorothiazide 25 mg, and simvastatin 20 mg.

In July 2016, the diabetologist decided to stop glimepiride and exenatide long-acting release and prescribed a sodium-glucose cotransporter-2 inhibitor (SGLT2i), dapagliflozin, 10 mg daily.

In his clinical history, he had started testosterone replacement therapy (TRT) 7 months before (testosterone undecanoate injection every 3 months) for primary hypogonadism due to a unilateral orchiectomy at the age of 16 years for cryptorchidism.

Three months after starting SGLT2i, he showed a 7.5-kg weight loss and good glycemic control. His blood tests showed a severe increase in hematocrit (Hct), Hb, and red blood cell (RBC) count. His total testosterone levels were in the normal range (Table 1). White blood cells and platelet counts were in the normal range.

Upon clinical examination, he appeared well. There were no signs of hypovolemia or dehydration. Vital signs were normal. Cardiopulmonary and abdominal evaluation showed no abnormalities.

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Abbreviations: EPO, erythropoietin; Hct, hematocrit; RBC, red blood cell; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; TRT, testosterone replacement therapy.

Table 1. Biochemical, Hormonal, and Anthropometrical Parameters of Patient 1

	Before Starting Testosterone Treatment (November 2015)	Starting Testosterone Therapy (December 2015)	Before Starting SGLT2i (May 2016)	Starting SGLT2i (July 2016)	3 mo After Starting SGLT2i (October 2016)	Testosterone Treatment Withdrawal (November 2016), Last Testosterone Injection: September 2016	7 mo After the Last Testosterone Injection (April 2017)
HbA_{1c}, %	7.2		7.8		6.9		7.1
Fasting glucose, mg/dL	192		139		158		145
BMI, kg/m^2	31.6		31.6		30.1		30.2
Hb, g/dL (NR: 13.5–18.0)	15.7		15.8		18.7–19.4		17.8
Hct, % (NR: 40.0–52.0)	45.9		45.1		55.8–57.1		53.2
RBC count, millions/m^3 (NR: 4.50–5.8)	5.1		5.1		6.9–6.1		5.8
Total testosterone, ng/mL (NR: 2.73–8.16)	2.12		4.72		5.41		2.23

Abbreviation: NR, normal range (according to the local laboratory).

As a precautionary measure, the andrologist decided to stop TRT and initiate acetylsalicylic acid, 100 mg daily. The patient was referred to a hematologist who performed a therapeutic phlebotomy to lower Hct. Molecular testing for JAK2 mutations was negative.

Seven months after the last testosterone undecanoate injection and 3 months after phlebotomy, in April 2017, Hb and Hct decreased but remained above the normal range (Table 1).

During the observation time, there were no reports of venous thromboembolism, myocardial infarction, or cerebrovascular accidents.

Case 2

I.M. is a 52-year-old nonsmoking man followed in our Andrology Unit for a primary hypogonadism after bilateral orchiectomy for two noncontemporary testicular cancers. He had been on TRT since 2012, first on transdermal formulation and then on intramuscular testosterone undecanoate (1000 mg every 10 to 12 weeks) with no adverse events.

He was diagnosed with T2DM in May 2016 with a medical history of class II obesity complicated by obstructive sleep apnea syndrome on continuous positive airway pressure treatment.

In September 2016, as his glycometabolic control was not on target, an SGLT2i, empagliflozin 10 mg daily, was prescribed, in addition to the pre-existing therapy with metformin 1000 mg/daily.

Four and 7 months after starting the therapy, good glycemic control and weight loss were achieved, respectively, but, simultaneously, severe increases in Hct, Hb, and RBCs were observed. White blood cells and platelet counts were in normal range at all time points. Total testosterone levels were in the low-normal range (Table 2). Obstructive sleep apnea syndrome was in good control with continuous positive airway pressure treatment, according to the pneumologist's periodical evaluation.

Upon clinical examination during the diabetologic follow-up, the patient appeared well with no evidence of hypovolemia or dehydration. Vital signs were normal. Cardiopulmonary and abdominal evaluation showed no abnormalities. There were no reports of venous thromboembolism, myocardial infarction, or cerebrovascular

Table 2. Biochemical, Hormonal, and Anthropometrical Parameters of Patient 2

	Before Starting SGLT2i (June 2016)	Starting SGLT2i (September 2016)	4 mo After Starting SGLT2i (January 2017)	7 mo After Starting SGLT2i (April 2017)	15 mo After Starting SGLT2i (December 2017)
HbA_{1c}, %	7.3		5.9	5.8	6.3
Fasting glucose, mg/dL	178		129	138	118
BMI, kg/m^2	35.6		34.7	34.1	35.0
Hb, g/dL (NR: 13.5–18.0)	16.2		17.2	16.7	16.9
Hct, % (NR: 40.0–52.0)	48.6		56.4	51.9	49.7
RBC count, millions/m^3 (NR: 4.50–5.8)	5.4		6.1	6.0	5.5
Total testosterone, ng/mL (NR: 2.73–8.16)	2.27			2.88	3.14

Abbreviation: NR, normal range (according to the local laboratory).

accidents. The diabetologist decided to continue the treatment with the SGLT2i, carefully monitoring Hct and Hb trends, and to temporarily increase the interval between the following testosterone injections. Follow-up hormonal data are reported in Table 2.

Discussion

Erythrocytosis is defined as Hct >53% or Hb >18.5 g/dL in men, corresponding to an erythrocyte mass >125% of that predicted for sex and body mass, although this definition may vary according to Ohlander *et al.* (1).

It can be a primary form, arising from a proliferation of erythrogenic precursors, or be a compensatory response to external stimuli leading to erythroid hyperplasia (secondary erythrocytosis). Erythrocytosis is associated with enhanced blood viscosity and platelet adhesiveness, leading to an increased cardiovascular risk (1, 2).

Testosterone treatment in hypogonadal men increases, up to 3.15 times, the risk of developing secondary erythrocytosis (3). This adverse effect is dose dependent and higher with short-acting rather than long-acting injectable T-esters and transdermal formulations (1, 4).

Potential mechanisms explaining the relationship between TRT and erythrocytosis include the direct stimulation of erythroid progenitor cells and increased production of erythropoietin (EPO) by the kidneys, but also the suppression of hepcidin, which subsequently results in augmented iron absorption and systemic transport, leading to enhanced erythropoiesis.

To date, no randomized or prospective studies have observed a direct relation between TRT-induced erythrocytosis and thromboembolic events (1, 3).

Nevertheless, frequent monitoring is recommended to avoid critically elevated levels, with 54% considered by the Endocrine Society as the Hct cutoff for TRT withdrawal (5).

An increase in Hct and Hb levels was also observed in patients with diabetes treated with SGLT2i, with only few cases of erythrocytosis (6, 7). This effect has been related to the diuretic action of SGLT2i, leading to decreased plasma volume and hemoconcentration, but other mechanisms, such as an increased production of EPO by renal fibroblasts, are also likely to play a role (8).

In fact, a tubular injury and an excessive glucose reabsorption occur in diabetes. Moreover, renal fibroblasts transform into dysfunctional cells with decreased EPO secretion, leading to nephrogenic anemia and kidney fibrosis. In this process, which is reversible until renal tubular injury is mild and not prolonged over time, SGLT2i reduce the amount of reabsorbed glucose in the proximal tubules, resulting in restoration of tubulointerstitial function and increased production of EPO by fibroblasts (9).

Moreover, the increased renal workload, due to the excessive glucose reabsorption in diabetes, causes higher oxygen consumption in the proximal tubules, resulting in hypoxia, oxidative stress, and a proinflammatory state that contribute to renal fibroblast dysfunction. Again, SGLT2i, by decreasing glucose reabsorption, may reverse these processes.

This is our report of cases of erythrocytosis during concomitant use of SGLT2i and TRT in patients with diabetes and hypogonadism. Both conditions, as explained previously, may have contributed to erythrocytosis, but we postulate that the combination of the two different drug mechanisms of action may have been decisive (Fig. 1).

The co-occurrence of T2DM and hypogonadism is known to be increasingly frequent: about one-third of men with T2DM and obesity have subnormal free testosterone concentration and need TRT (10).

Given the frequent association between male hypogonadism and T2DM and the availability of SGLT2i as a new class of glucose-lowering agents, diabetologists and andrologists should bear in mind the increased risk of erythrocytosis during the simultaneous use of testosterone and these new antidiabetic drugs.

Both patients provided written informed consent for the publication of these case reports.

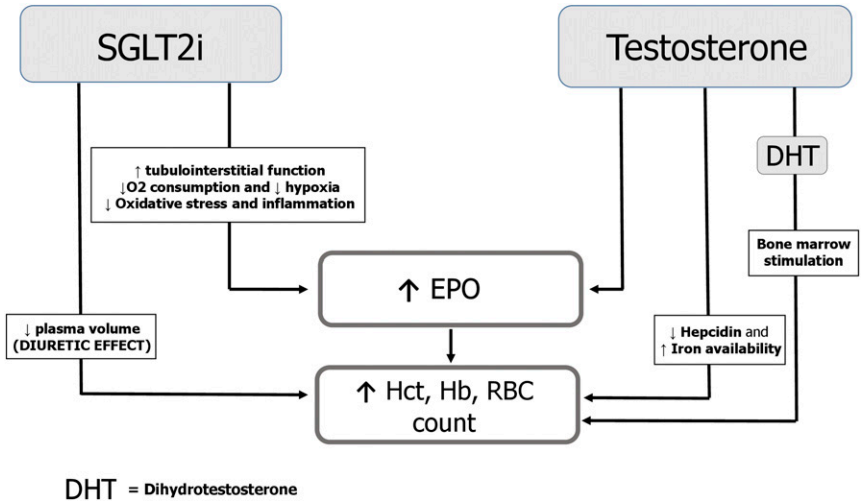

Figure 1. Mechanism proposed for erythrocytosis during concomitant use of SGLT2i and TRT.

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