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Letter to the Editor

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Increased Hematocrit During Sodium-Glucose Cotransporter-2 Inhibitor Therapy

Samuel N. Heyman[a, e], Mogher Khamaisi[b], Christian Rosenberger[c], Auryan Szalat[a], Zaid Abassi[d]

To the Editor

Treatment with sodium-glucose cotransporter-2 (SGLT-2) leads to increased hematocrit. Other than hemoconcentration, this phenomenon could be attributed to enhanced erythropoiesis, as indicated by a rise in plasma erythropoietin (EPO) and reticulocytosis [1]. SGLT-2 inhibitors lead to improved renal cortical oxygenation, reflecting reduced transport activity in proximal tubules [2]. In their recent article in JOCMR, Sano et al proposed that improved survival of cortical peritubular interstitial cells with improved cortical oxygenation is the cause of increased EPO with SGLT-2 inhibition [3]. While this hypothesis is interesting, it is not evidence-based, and we would like to propose a more likely alternative explanation, in line with the current understanding of EPO regulation [4], namely intensified hypoxia at the renal cortico-medullary junction.

EPO is a hypoxia-triggered gene, up-regulated by hypoxia-inducible factors (HIFs). HIFs are heterodimers consisting of α and β sub-units, that upon attachment to hypoxia response elements along nuclear DNA strands induce trans-activation of numerous HIF-dependent genes, including EPO [4]. Under normoxic conditions, cytoplasmic HIF-α subunits undergo proteasomal degradation, permeated by specific HIF-prolyl hydroxylases. These enzymes are inhibited under hypoxic conditions, leading to cytoplasmic accumulation of HIF-α subunits. Consequently, HIF-α subunits undergo nuclear translocation and binding with HIF-β subunits, promoting HIF-mediated gene responses [4].

Renal parenchymal oxygenation declines in the diabetic kidney under experimental settings, reaching 10 mm Hg at the cortico-medullary junction [5]. We have previously reported that such intensified hypoxia in the diabetic rat kidney leads to stabilization of α subunits of HIF-2 isoforms in peritubular interstitial cells within the deep cortex and the outer medulla, leading to nuclear immunostaining of HIF-2 [6] and that these cells are the origin of EPO upon HIF-2 stabilization [7]. Furthermore, HIF-prolyl hydroxylases have recently been shown to trigger EPO and erythropoiesis in phase 2 clinical trials [8].

While cortical oxygenation improves with SGLT-2 inhibition, medullary oxygenation substantially declines, both in diabetic and in intact rats, conceivably due to increased solute delivery to distal tubular segments, with enhanced regional oxygen expenditure for tubular transport [2]. Therefore, intensified hypoxia at the deep cortex and outer medulla induced by SGLT-2 inhibition is likely the cause of enhanced EPO transcription and consequent reticulocytosis.

Another observation in line with this narrative is the reversal of post-renal transplantation erythrocytosis with angiotensin II inhibition [9], conceivably reflecting attenuation of renal parenchymal hypoxia by blocking the renin-angiotensin-aldosterone axis (RAAS).

Taken together, we conclude that increased EPO levels and erythropoiesis following SGLT-2 inhibition likely result from enhanced hypoxia at the renal cortico-medullary junction, rather than through the amelioration of cortical oxygenation, as suggested by Sano et al [3].

References

1. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab. 2013;15(9):853-862.
2. O'Neill J, Fasching A, Pihl L, Patinha D, Franzen S, Palm F. Acute SGLT inhibition normalizes O2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol. 2015;309(3):F227-234.
3. Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased Hematocrit During Sodium-Glucose Cotransporter 2 Inhibitor Therapy Indicates Recovery of Tubulointerstitial Function in Diabetic Kidneys. J Clin Med Res. 2016;8(12):844-847.
4. Haase VH. Regulation of erythropoiesis by hypoxia-in-

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[a]Division of Medicine, Hadassah Hebrew University Hospitals, Jerusalem, Israel
[b]Division of Medicine, Rambam Medical Center, Haifa, Israel
[c]Department of Nephrology, Charite Hospital, Berlin, Germany
[d]Department of Physiology, Bruce Rappaport Faculty of Medicine, Technion-ITT, Haifa, Israel
[e]Corresponding Author: Samuel Heyman, Department of Medicine, Hadassah Hebrew University Hospital, Mt. Scopus, PO Box 24035, Jerusalem 91240, Israel. Email: heyman@cc.huji.ac.il

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ducible factors. Blood Rev. 2013;27(1):41-53.
5. Palm F, Cederberg J, Hansell P, Liss P, Carlsson PO. Reactive oxygen species cause diabetes-induced decrease in renal oxygen tension. Diabetologia. 2003;46(8):1153-1160.
6. Rosenberger C, Khamaisi M, Abassi Z, Shilo V, Weksler-Zangen S, Goldfarb M, Shina A, et al. Adaptation to hypoxia in the diabetic rat kidney. Kidney Int. 2008;73(1):34-42.
7. Paliege A, Rosenberger C, Bondke A, Sciesielski L, Shina A, Heyman SN, Flippin LA, et al. Hypoxia-inducible factor-2alpha-expressing interstitial fibroblasts are the only renal cells that express erythropoietin under hypoxia-inducible factor stabilization. Kidney Int. 2010;77(4):312-318.
8. Wyatt CM, Drueke TB. HIF stabilization by prolyl hydroxylase inhibitors for the treatment of anemia in chronic kidney disease. Kidney Int. 2016;90(5):923-925.
9. Esposito R, Giammarino A, De Blasio A, Martinelli V, Cirillo F, Scopacasa F, Federico S, et al. Ramipril in post-renal transplant erythrocytosis. J Nephrol. 2007;20(1):57-62.