Received: 2 June 2022 | Revised: 5 August 2022 | Accepted: 10 August 2022

DOI: 10.1111/dom.14836

RESEARCH LETTER

WILEY

Predictors of haemoglobin levels and of changes in these levels, focusing on anaemia and polycythaemia after administration of the sodium-glucose cotransporter-2 inhibitor tofogliflozin

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Funding information
None.

1 | INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been reported to increase haemoglobin (Hb) and haematocrit (Ht) levels in type 2 diabetes (T2D).[1] Recent studies suggested that SGLT2 inhibitors might correct anaemia[2] in T2D. Increases in Hb in relation to enhanced oxygen supply in circulating plasma might contribute to the SGLT2 inhibitor-induced prevention of cardio-renal events in T2D.[3,4]

It has been reported, however, that not only anaemia, but also polycythaemia increases the risk of mortality and worsening heart failure.[5] A recent study reported that SGLT2 inhibitor use in 30 patients was associated with erythrocytosis, and that 26 of these patients (87%) were treated for polycythaemia and four (13%) developed thrombosis.[6] Some patients with T2D have polycythaemia associated with obesity and/or fatty liver (FL).[7] It would be clinically meaningful to investigate the impact of SGLT2 inhibitors on Hb in individuals with T2D and polycythaemia. The clinical predictors of Hb values after SGLT2 inhibitor therapy are little known; therefore, the present study examined the impact of the SGLT2 inhibitor tofogliflozin on Hb and explored factors that influence tofogliflozin-mediated changes in Hb, focusing on anaemia and polycythaemia in T2D.

2 | METHODS

A post hoc analysis was conducted of two tofogliflozin Phase 3 studies (monotherapy and add-on therapy) of individuals with T2D who underwent 52 weeks of tofogliflozin treatment and then 2 weeks of observation after its discontinuation.[8] A total of 774 patients were included. Details of both Phase 3 studies were previously reported[8] and some are noted in the Supplementary Appendix. Data from these periods were used for the present analysis.

TABLE 1 Baseline values for study participants according to baseline hemoglobin levels

	Anemia ($n = 34$)	Normal Hb ($n = 685$)	Polycythemia ($n = 55$)	p value
Age (years)	63.1 (9.6)	58.7 (10.4)	53.6 (10.1)	<0.001
Men/women, *n* (%)	15 (44.1)/19 (55.9)	446 (65.1)/239 (34.9)	50 (90.9)/5 (9.1)	<0.001
TOFO (20 mg/40 mg), *n* (%)	9 (26.5)/25 (73.5)	207 (30.2)/478 (69.8)	19 (34.5)/36 (65.5)	0.694
Concomitant antidiabetic drugs, *n* (%)	24 (70.6)	525 (76.6)	35 (63.6)	0.082
Monotherapy/sulfonylureas/glinides/biguanides/pioglitazone/a-glucosidase inhibitors/dipeptidyl peptidase-4 inhibitors, *n* (%)	10 (29.4)/7 (20.6)/0 (0.0)/1 (2.9)/6 (17.6)/4 (11.8)/6 (17.6)	160 (23.4)/147 (21.5)/21 (3.1)/93 (13.6)/89 (13.0)/85 (12.4)/90 (13.1)	20 (36.4)/12 (21.8)/1 (1.8)/4 (7.3)/4 (7.3)/7 (12.7)/7 (12.7)	-
Concomitant antihypertensive drugs, *n* (%)	16 (47.1)	327 (47.7)	23 (41.8)	0.721
ARB/ACE-I/CCB/Diuretics, *n* (%)	13 (38.2)/1 (2.9)/9 (26.5)/4 (11.8)	245 (35.8)/17 (2.5)/198 (28.9)/59 (8.6)	17 (30.9)/0 (0.0)/11 (20.0)/1 (1.8)	-
Concomitant antihyperlipidemic drugs, no. (%)	17 (50.0)	343 (50.1)	21 (38.2)	0.239
Statin/ezetimibe/ω-3/fibrate/nicotinic acid	16 (47.1)/2 (5.9)/0 (0.0)/1 (2.9)/0 (0.0)	286 (41.8)/32 (4.7)/10 (1.5)/41 (6.0)/9 (1.3)	16 (29.1)/3 (5.5)/2 (3.6)/6 (10.9) 2 (3.6)	-
Duration of diabetes (years)	7.9 (6.7)	7.2 (5.9)	5.8 (4.8)	0.184
HOMA-IR	2.0 (1.3)	3.2 (2.3)	4.2 (2.6)	<0.001
HOMA-β	28.1 (18.5)	33.8 (26.0)	33.8 (41.6)	0.480
Systolic blood pressure (mmHg)	129.3 (14.5)	130.6 (14.0)	128.2 (14.4)	0.433
Diastolic blood pressure (mmHg)	71.4 (10.9)	77.5 (10.1)	79.0 (9.5)	0.002
BMI (kg/m^2)	23.7 (4.0)	25.6 (4.3)	26.8 (3.6)	0.004
Baseline BMI ≥ 25 kg/m^2, *n* (%)	9 (26.5)	323 (47.2)	38 (69.1)	<0.001
BMI at week 52 ≥ 25 kg/m^2, *n* (%)	6 (19.4)	219 (36.0)	25 (54.3)	0.006
Body weight (kg)	59.3 (12.3)	68.3 (14.0)	75.0 (12.2)	<0.001
Waist circumference (cm)	84.0 (11.1)	89.6 (10.3)	92.8 (9.1)	<0.001
Fasting insulin (pmol/L)	33.3 (18.5)	48.8 (33.3)	57.5 (43.7)	0.004
Triglycerides (mg/dl)	103.5 (60.0–127.0)	115.0 (83.0–168.0)	176.0 (116.0–267.0)	-
Ln-Triglycerides (ln[mg/dl])	4.5 (0.5)	4.8 (0.5)	5.2 (0.6)	<0.001
Triglycerides (mmol/L)	1.2 (0.7–1.4)	1.3 (0.9–1.9)	2.0 (1.3–3.0)	<0.001
HDL-C (mg/dl)	63.6 (16.6)	61.0 (17.1)	51.3 (13.3)	<0.001
HDL-C (mmol/L)	1.6 (0.4)	1.6 (0.4)	1.3 (0.3)	<0.001
LDL-C (mg/dl)	109.9 (24.8)	124.3 (29.4)	123.9 (29.9)	0.021
LDL-C (mmol/L)	2.8 (0.6)	3.2 (0.8)	3.2 (0.8)	0.021
Fatty liver index	25.7 (25.4)	43.1 (27.7)	61.8 (23.2)	<0.001
Estimated fatty liver, *n* (%)	13 (38.2)	411 (60.0)	49 (89.1)	<0.001
Estimated fatty liver at week 52, *n* (%)	6 (19.4)	271 (44.6)	29 (64.4)	<0.001
GGT (IU/L)	23.5 (13.2)	46.2 (47.4)	65.9 (46.9)	<0.001
AST (IU/L)	23.6 (5.2)	26.4 (10.5)	30.9 (16.4)	0.003
ALT (IU/L)	20.2 (9.8)	29.0 (15.6)	38.8 (18.9)	<0.001
eGFR ($ml/min/1.73m^2$)	75.1 (17.2)	83.9 (18.3)	88.7 (18.4)	0.003
UACR (mg/g Cr)	19.4 (11.1–64.5)	15.7 (8.7–41.9)	31.5 (14.2–80.1)	-
Ln-UACR (ln[mg/g Cr])	3.2 (1.1)	3.1 (1.3)	3.7 (1.5)	0.002
Urinary NAG (U/g Cr)	8.6 (5.4–13.9)	6.9 (5.0–10.5)	8.4 (5.9–12.8)	-
Ln-urinary NAG (ln[U/g Cr])	2.2 (0.5)	2.0 (0.6)	2.1 (0.6)	0.021
Urinary beta2MG (μg/g Cr)	149.7 (92.1–279.8)	131.5 (78.2–243.0)	134.8 (69.2–262.3)	-
Ln-urinary beta2MG (ln[μg/g Cr)])	5.1 (1.0)	5.0 (1.0)	5.0 (1.0)	0.697

TABLE 1 (Continued)

	Anemia ($n = 34$)	Normal Hb ($n = 685$)	Polycythemia ($n = 55$)	p value
HbA1c (%)	7.7 (0.9)	8.0 (0.9)	8.3 (1.1)	0.012
HbA1c (mmol/mol)	61.1 (10.0)	64.4 (9.7)	67.5 (12.0)	0.012
Fasting plasma glucose (mg/dl)	145.9 (40.6)	159.9 (36.0)	181.4 (37.8)	<0.001
BNP (pg/ml)	14.2 (10.0–29.2)	10.7 (6.2–18.6)	8.2 (4.0–14.4)	-
Ln-BNP (ln[pg/ml])	2.8 (0.7)	2.4 (0.7)	2.1 (0.8)	<0.001
Hematocrit (%)	35.3 (1.7)	42.8 (3.1)	50.0 (2.1)	<0.001
Hemoglobi *n* (g/L)	118.1 (6.8)	145.4 (10.7)	171.5 (5.9)	<0.001
Red blood cells (10^4/μl)	395.5 (40.5)	455.6 (34.9)	532.4 (29.2)	<0.001
White blood cells (/μl)	5541.2 (1802.5)	5920.1 (1606.0)	6385.5 (1977.2)	0.047

Estimated anaemia group was defined according to the World Health Organization as Hb levels <130 g/dL in men and < 120 g/dL in women.
Estimated polycythaemia group was defined as Hb >165 g/L in men and > 16 g/L in women.
Normal Hb group was defined as Hb 130-165 g/L in men and 120-160 g/L in women.
$\text{FLI} = (e^{0.953 \times \text{Ln (Triglycerides)} + 0.139*\text{BMI} + 0.718*\text{Ln (GGT)} + 0.053 \times \text{waist circumference} - 15.745}) /$
$(1 + e^{0.953 \times \text{Ln (Triglycerides)} + 0.139 \times \text{BMI} + 0.718 \times \text{Ln (GGT)} + 0.053 \times \text{waist circumference} - 15.745}) \times 100.$
An FLI ≥35 for males and ≥ 20 for females determined the presence of FL, while an FLI <35 for males and < 20 for females ruled out FL.
Data are expressed as mean (standard deviation) or median (interquartile range).
Analysis of variance between three groups.
ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; beta2MG, beta-2 microglobulin; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; FL, fatty liver; FLI, fatty liver index; GGT, gamma-glutamyltranspeptidase; Hb, haemoglobin; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; Ht, haematocrit; LDL, low-density lipoprotein; Ln-, Ln-transformed-; NAG, N-acetyl-beta-d-glucosaminidase; TOFO, tofogliflozin; UACR, urine albumin-to-creatinine ratio.

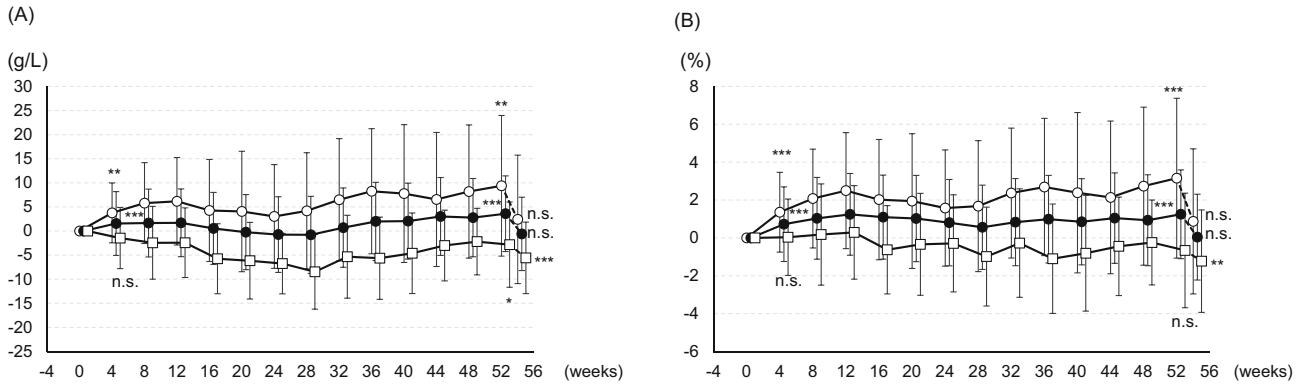

FIGURE 1 Changes in haemoglobin (Hb), haematocrit (Ht) and red blood cells from baseline to Week 52 and 2 weeks after discontinuation of tofogliflozin therapy according to baseline Hb level. (A) Changes in Hb from baseline to Week 4, Week 52 and Week 54 (2 weeks after discontinuation of tofogliflozin therapy) according to baseline Hb levels. (B) Changes in Ht from baseline to Week 4, Week 52 and Week 54 (2 weeks after discontinuation of tofogliflozin therapy) according to baseline Hb level. Data are expressed as mean (standard deviation). ◦ Anaemia; ● Normal Hb; □ Polycythaemia. Participants were divided into anaemia (baseline Hb <130 g/L in men and < 120 g/L in women, n = 34), polycythaemia (> 165 g/L in men and > 160 g/L in women, n = 55), and normal Hb (n = 685) groups. Solid line, tofogliflozin therapy term; dotted line, after tofogliflozin therapy. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, n.s. not significant vs. baseline.

The two Phase 3 studies were reviewed and approved by the institutional review boards of each participating centre. All participants provided written informed consent prior to enrolment. The present study was also reviewed and approved by the Ethics Committee of Niigata University, and we applied the opt-out method to obtain consent using the Niigata University website.

Definitions of baseline values are provided in the Supplementary Appendix. Participants were divided into three groups according to baseline Hb level (Table 1): anaemia (baseline Hb <130 g/L in men and < 120 g/L in women),[9] polycythaemia (>165 g/L in men and > 160 g/L in women),[10] and normal Hb. Demographics were summarized with appropriate descriptive statistics (means and standard deviation for continuous variables and numerals and percentages for categorical variables).

We also re-categorized the participants according to Hb values at Week 52 based on the above-mentioned cut-off values.

Differences in baseline and Week 52 assessments among groups were analysed using one-way analysis of variance or

Fisher's exact test. Changes in variables from baseline to Week 52 and Week 52 to Week 54 (2 weeks after discontinuation of tofogliflozin) were analysed using a paired t-test. Analyses of correlations of combinations among changes in other variables from baseline to Week 52 were performed using Spearman rank-order correlation coefficients. To identify baseline clinical factors that might affect Hb from baseline to Week 4 and Week 52, 23 clinically significant baseline variables (listed in the Supplementary Appendix) were included as potential factors in a generalized linear model. The generalized linear model was followed by stepwise model selection for factors with P values <0.05. All data were analysed using the SAS System, Release 9.3 (SAS Institute, Cary, North Carolina). The (two-sided) significance level for each test was 0.05 unless otherwise specified. No multiple comparisons or multiplicity adjustments were performed.

3 | RESULTS

Baseline characteristics of study participants according to baseline Hb levels are shown in the Table 1. Baseline values for triglycerides and hepatic enzymes, percentage of patients with estimated FL according to the FL index (FLI),[11] and values related to insulin resistance were highest in the polycythaemia group.

Haemoglobin had significantly changed at Week 52 in the anaemia (mean + 9.39 [14.59] g/L; $P < 0.01$ vs. baseline), normal Hb (+3.60 [7.85], $P < 0.001$) and polycythaemia groups (−2.82 [8.84]; $P < 0.05$). After discontinuation of tofogliflozin for 2 weeks, the significant reduction in Hb was maintained in the polycythaemia group but Hb returned to baseline levels in the other two groups (Figure 1). Other changes in variables are shown in Supplemental Table 1. Change in Hb was significantly correlated with Ln-triglycerides (rho = 0.42, $P = 0.005$) and with FLI (rho = 0.38, $P = 0.012$) at Week 52 in the polycythaemia group but not in the anaemia and normal Hb groups (Supplemental Figure 1 and Supplemental Table 2).

Results of the generalized linear model used to predict factors that influenced changes in Hb from baseline to Week 4 and to Week 52 are shown in Supplemental Table 3. Higher brain natriuretic peptide (BNP) and lower Ht levels were predictors of an initial increase in Hb. However, baseline BNP and Ht levels were not observed to be predictors of chronic increases in Hb levels. Conversely, higher baseline Hb levels were independently correlated with larger chronic decreases in Hb levels.

The results of the reclassification of participants according to Hb values measured at Week 52 are shown in Supplementary Table 4.

4 | DISCUSSION

The present study clarified that SGLT2 inhibitors do not always increase Hb levels but sometimes decrease those values in cases of polycythaemia in association with variables reflecting FL and lipid levels.

As shown previously, an initial volume reduction[12] and increases in erythropoietin[1] resulting from SGLT2 inhibitor use might influence the increases in Hb levels associated with tofogliflozin. Interestingly, higher baseline Hb levels were independently correlated with larger chronic decreases in Hb levels.

Higher Hb levels were reported to be correlated with a higher prevalence of FL in T2D.[7] Similar results were obtained in the participants of the present study. SGLT2 inhibitors were reported to reduce visceral fat including fat in liver.[13,14] According to the present results, the improvement in variables associated with FL might have caused the Hb reductions in the polycythaemia group after 52 weeks of tofogliflozin therapy. Furthermore, higher triglyceride levels (correlated with fat accumulation in liver[15]) were independently correlated with greater Hb reductions. Therefore, improvements in liver steatosis could cause reductions in Hb levels. Specifically in polycythaemia, the positive correlations of reductions in Hb with reductions in triglycerides and the FLI might support that hypothesis. Interestingly, it was reported that Hb reductions might be induced not by haemodilution after treatment with pioglitazone[16] (improvement of FL has been reported[15]). Further studies will be needed to clarify the association of Hb reductions, especially in polycythaemia, with the correction of FL, including assessment of intrahepatic fat content measured by direct methods and analysis of the association between Hb and changes in intrahepatic fat content resulting from bariatric surgery or use of agents reported to improve FL (glucagon-like peptide-1 analogues, pioglitazone, etc.).[15]

The present study has some limitations. First, it was a post hoc analysis. Second, we did not perform a comparison between placebo and tofogliflozin. Third, we did not have information on smoking status. Fourth, measurements in relation to erythropoiesis and iron metabolism could not be performed. Fifth, we did not evaluate diet, food preferences, and dietary changes. Sixth, we could not directly measure intrahepatic fat content; therefore, we could not distinguish which components of the FLI (body mass index, waist circumference, triglycerides, etc.) or hepatic fat were correlated with Hb (or Hb change via tofogliflozin).

Haemoglobin levels may approach normal in both polycythaemia and anaemia after tofogliflozin therapy. Lowering of triglycerides in relation to improved FL may be related to correction of higher Hb levels in polycythaemia.

AUTHOR CONTRIBUTIONS

H. Suganami had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Y. Matsubayashi contributed to the interpretation of data, writing of the first draft, and revision of the manuscript for important intellectual content. H. Sone, K. Fujihara, K. Kaku, T. Yamada, Y. Yaguchi, T. Sato, M. Oe and A. Yoshida revised the manuscript for important intellectual content. H. Suganami created the database, performed statistical analyses, and contributed to the interpretation of the data. S. Tanaka conducted a secondary check of the integrity of the data and accuracy of the data analysis from a fair perspective as a

third party. All authors have read and approved the final manuscript for submission.

ACKNOWLEDGMENTS

We sincerely thank all participants in the tofogliflozin studies. The original Phase 3 studies of tofogliflozin were funded by Chugai Pharmaceutical Pharmaceutical Co., Ltd.

CONFLICT OF INTEREST

Y. Matsubayashi, T. Sato, Y. Yaguchi, K. Fujihara, T. Yamada and S. Tanaka report no conflicts of interest regarding the work presented. A. Yoshida, M. Oe and H. Suganami are employees of Kowa Co., Ltd. K. Fujihara has received donations for research from Eli Lilly and Takeda. H. Sone has received donations for research from Astellas, Eli Lilly, Kowa, Kyowa Hakko Kirin, MSD, Japan Blood Products Organization, Boehringer Ingelheim, Pfizer, Novartis, Sumitomo Dainippon, Otsuka, Sanofi, Mitsubishi Tanabe, Asahi Kasei, Meiji Seika, Eisai, Yakult, Takeda, Taishotoyama and Daiichi Sankyo. K. Kaku has been an advisor to and received honoraria for lectures from Astelas, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical, MSD, Kowa, Kissei, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Daiichi Sankyo and Sanofi.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14836.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Matsubayashi Y, Yoshida A, Suganami H, et al. Predictors of haemoglobin levels and of changes in these levels, focusing on anaemia and polycythaemia after administration of the sodium-glucose cotransporter-2 inhibitor tofogliflozin. *Diabetes Obes Metab*. 2022;24(12):2469-2473. doi:10.1111/dom.14836