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Original Article

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Increased Transferrin Concentrations Are Not Associated With Thrombosis in People Living at High Altitude

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Abstract

Background: Bolivian Andean Aymara highlanders, living at 4,000 m for 14,000 years, have evolved genetic adaptations to hypoxia. These include *EGLN1* encoding prolyl hydroxylase 2 (PHD2), a regulator of transferrin transcription. Transferrin level increases in hypoxia and iron deficiency. Contrasting reports indicate that elevated transferrin is associated with experimentally induced thrombosis in mice undergoing short-stay at high altitude, but with decreased thrombosis in a congenital disorder of hypoxia-sensing.

Methods: A retrospective study was conducted in people living at high altitude (3,650 - 4,150 m). We analyzed serum transferrin concentration and thrombosis history in Aymara patients with high-altitude erythrocytosis (n = 149, median age 55 years, female gender 30%, iron deficiency 23%) or high-altitude anemia (n = 137, median age 43 years, female gender 86%, iron deficiency 57%).

Results: The median transferrin concentration was 339 mg/dL in erythrocytosis patients versus 310 mg/dL in anemia patients (P = 0.037); it was 367 mg/dL in iron deficient versus 312 mg/dL in iron replete patients (P < 0.001). Thrombosis history was present in 13% of erythrocytosis and 8% of anemia patients (P = 0.25) and was present in 16% of iron deficient and 7% of iron replete patients (P = 0.017). After adjustment for erythrocytosis and iron deficiency in multivariate regression analysis, the mean (95% confidence interval) transferrin concentration was 277 (237 - 316) mg/dL in 30 patients with thrombosis history versus 324 (306 - 341) mg/dL in 256 patients without thrombosis history (P = 0.018). Similar trends occurred for the subgroups of arterial thrombosis history (P = 0.044) and venous thrombosis history (P = 0.22).

Conclusions: In individuals with extreme environmental hypoxia, we found no evidence that increased transferrin is associated with increased thrombosis history. Rather, we observed a trend to decreased thrombosis history with increased transferrin levels.

Keywords: Transferrin; Ferritin; Iron deficiency; Thrombosis; Hypoxia; High altitude

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Introduction

Native Bolivian Aymaras have lived at approximately 4,000 m in the Andes Mountains for about 14,000 years, exposed to low atmospheric pressure and a corresponding decrease in atmospheric partial pressure of oxygen, i.e., hypobaric hypoxia. Evolutionary genetic adaptation to high altitude in Aymara Andeans involves cardiovascular system genes [1], with less prominent selection of hypoxia-inducible factor (HIF) pathway genes including *EPAS1* encoding HIF-2α and *EGLN1* encoding prolyl hydroxylase 2 (PHD2) [2]. *HIF1A* is also upregulated at high altitude [3, 4] and correlates with an Aymara evolutionary-selected *NFKB1* haplotype encoding loss of function alternate *NFKB1* transcripts that augment both HIFs and inflammation [5].

HIFs activate the transcription of genes that increase oxygen delivery and facilitate metabolic adaptation to hypoxia. There are three HIFs, HIF-1, HIF-2, and HIF-3, with HIF-1 and HIF-2 the best studied. HIFs are composed of α and β subunits. PHD2 is an iron-, α-ketoglutarate-, and oxygen-dependent enzyme that decreases HIFs by hydroxylating HIF-α subunits, a step that enables HIF recognition by von Hippel-Lindau (VHL) protein and its subsequent proteasomal degradation [6].

Transferrin, which is responsible for iron transport in the blood and iron delivery to cells through transferrin receptor-mediated endocytosis, is induced by both hypoxia and iron deficiency via HIF-1 [7]. Transferrin levels are increased in people who live at high altitude [8]. Iron deficiency itself is a risk factor for thrombosis as recently reviewed [9].

Native Andeans are primarily composed of two large groups, Aymaras predominating in Bolivia and Argentina and Quechuas predominating in Peru, Chile, and Ecuador. Both groups have adapted by increased hemoglobin concentrations compared to sea-level inhabitants. Normal hemoglobin levels in healthy highlanders range from 15 - 18 g/dL in males and 14 - 17 g/dL in females, which are 3 - 4 g/dL higher than sea-level values [10, 11]. Andeans may be predisposed to thromboembolic complications as environmental hypoxia is an independent risk factor for postoperative deep vein thrombosis and pulmonary embolism in persons living at high altitude [12], and for venous and arterial thrombosis in lowlander persons who move from low to high altitude [13]. While Quechuas and Aymaras share some evolutionary genetic adaptations, others differ between the Quechuas [14] and the Aymaras [1]. To date, no evidence has been published of increased thromboembolism in Bolivian Aymaras living at 4,000 m versus those living at sea level [12].

It has recently been proposed that the plasma iron transporter, transferrin, is a prothrombotic protein that promotes blood coagulation when abnormally increased [15, 16]. Specifically, it was reported that transferrin induces hypercoagulability by potentiating thrombin/factor XIIa interaction and by inhibiting antithrombin [15]. Furthermore, it was proposed that this mechanism contributes to thromboembolism at high altitude [8], and that pharmacological blockade or neutralization of transferrin may reverse the increased coagulation tendency observed under hypoxic conditions. Mice kept in hypoxic conditions had increased thrombosis in carotid arteries and deep veins, which could be reversed with anti-transferrin antibodies and peptides that block transferrin binding to thrombin and FXIIa [8]. However, a prospective study of 155 people with Chuvash erythrocytosis, a condition with genetically augmented hypoxic responses at normal altitude and ambient O_2 [17], reported that elevated transferrin was associated with reduced thrombosis. Chuvash erythrocytosis is the first described inherited condition with augmented HIF levels [18], and thromboses are the principal cause of morbidity and mortality [19]. Other studies have also provided evidence for a protective role of transferrin against thrombosis [20, 21].

In the present report, we examine the relationship of increased circulating transferrin concentrations with a history of clinically documented thrombosis under the extreme conditions of high altitude with or without concomitant iron deficiency.

Materials and Methods

This retrospective study was conducted in people living at high altitude in two locations in Bolivia from January 2018 to September 2023: La Paz (11,942 ft, 3,650 m) and its suburb El Alto (13,615 ft, 4,150 m). We analyzed the relationship of serum transferrin concentration with history of thrombosis in Aymaras born and residing at these two high altitudes, who were found to have anemia (n = 137) or increased hemoglobin (n = 149). Anemia was defined as hemoglobin < 13 g/dL in women and < 14 g/dL in men (high-altitude anemia), and erythrocytosis was defined as hemoglobin levels > 18 g/dL in women and > 19 g/dL in men (high-altitude erythrocytosis) [10]. Iron deficiency was defined as serum ferritin < 30 µg/L and mean corpuscular volume (MCV) < 80 fL (thalassemia is not present in Andean South American regions) [22]. Echo-Doppler study records validated thrombotic events. Thromboses were categorized as venous (deep vein thrombosis, pulmonary thromboembolism and retinal) or arterial (ischemic stroke, acute myocardial infarction and mesenteric). This study was approved by the Institutional Ethics Committee of San Andres University School of Medicine and adhered to the principles set forth in the Declaration of Helsinki.

Data analysis was performed through Excel 16.29.1, SPSS, and SYSTAT programs. The association of serum transferrin with a history of thrombosis was tested by multivariate linear regression modeling, where covariates were determined by forward-backward model selection on variables which are individually correlated with serum transferrin or with a history of thrombosis at P = 0.1.

Clinical evaluations, laboratory tests, and echo-Doppler studies were performed in the routine care of patients not with the goal of testing a research hypothesis.

Results

There were 19 men and 118 women with high-altitude anemia, and 105 men and 44 women with high-altitude erythrocytosis, all with serum transferrin concentration measurements (Supplementary Material 1, jh.elmerpub.com). The 137 patients with high-altitude anemia were younger than the 149 patients with high-altitude erythrocytosis (median (interquartile range (IQR)) age of 43 (33 - 55) years versus 55 (49 - 64) years, P < 0.001), and they were more often females, 86% in the anemia cohort versus 30% in the erythrocytosis cohort (P < 0.001). Iron deficiency (defined by serum ferritin < 30 µg/L and MCV < 80 fL) was present in 57% of the patients with anemia versus 23% of those with erythrocytosis (P < 0001). Transferrin levels were slightly lower in anemia patients (median (IQR): 310 (210 - 401) mg/dL versus 339 (294 - 371) mg/dL in erythrocytosis patients, P = 0.037). A history of thrombosis, mainly venous, was present in 8.0% of the anemia patients compared to 13.0% of the erythrocytosis patients (P = 0.25). The history of venous thrombosis was found in 5.1% of the high-altitude anemia patients and 8.7% of the high-altitude erythrocytosis patients (P = 0.25). The history of arterial thrombosis was found in 3.7% of the high-altitude anemia patients and 4.0% of the high-altitude erythrocytosis patients (P = 1.0). One patient had a history of both venous and arterial thrombosis.

Transferrin levels were higher in the iron deficiency patients (median (IQR): 367 (278 - 426) mg/dL versus 312 (253 - 360) mg/dL in the iron replete patients, P < 0.001). A history of thrombosis was present in 16% of the iron deficiency patients compared to 6.9% of the iron replete patients (P = 0.017). The history of venous thrombosis was found in 9.8% of iron deficiency patients and 5.2% of iron replete patients (P = 0.16). The history of arterial thrombosis was found in 6.3% of the iron deficiency patients and 2.3% of the iron replete patients (P

Table 1. Demographics, Laboratory Studies, and Iron Status in 286 High Altitude Patients, 137 With Anemia and 149 With Erythrocytosis, According to the History of Thrombosis

Baseline variable	No thrombosis history		History of thrombosis present		P value
	Median (IQR) or n (%)	N	Median (IQR) or n (%)	N	
Demographics					
High altitude anemia	126 (49.2%)	256	11 (36.7%)	30	0.25
Age (years)	49 (41 - 58)	256	65 (56 - 74)	30	< 0.001
Female gender	149 (58.2%)	256	13 (43.3%)	30	0.13
Blood count					
MCV (fL)	85.5 (70.5 - 91.6)	256	75.5 (69.3 - 86.2)	30	0.20
WBC (/µL)	5,685 (4,770 - 6,908)	256	5,600 (4,595 - 7,200)	30	0.60
Neutrophils (/µL)	3,365 (2,700 - 4,132)	256	3,850 (2,950 - 4,712)	30	0.055
Lymphocytes (/µL)	1,895 (1,400 - 2,275)	256	1,315 (1,100 - 1,722)	30	< 0.001
Platelets ($\times 10^3$/µL)	235 (167 - 325)	255	204.5 (171 - 249)	30	0.32
Iron metabolism					
Iron (µg/dL)	68.5 (31.75 - 106)	240	45 (17.5 - 88.4)	29	0.11
Ferritin (ng/mL)	34 (11 - 99)	256	14 (7 - 45)	30	0.030
Iron deficiency	94 (36.7%)	256	18 (60%)	30	0.017
Transferrin (mg/dL)	334 (262 - 387)	256	304 (242 - 358)	30	0.25

Median (IQR) or n (%) of covariates are presented according to thrombosis history. P values were estimated using linear regression for continuous variables and Fisher's exact test for binary variables. WBC, neutrophils, lymphocytes, and iron were square root transformed; platelets and ferritin were logarithm transformed. WBC: white blood cell; MCV: mean corpuscular volume; IQR: interquartile range.

= 0.12) (Supplementary Material 2, jh.elmerpub.com).

We assessed the correlations of baseline characteristics with history of thrombosis, as shown in Table 1. Older age, lower lymphocyte count, iron deficiency, and lower serum ferritin were significantly associated with the history of thrombosis. We also assessed the correlation of these baseline characteristics with transferrin concentrations. As shown in Table 2, only high-altitude erythrocytosis versus anemia, low MCV, iron deficiency, and low serum ferritin, had significant associations with higher serum transferrin concentration.

We then assessed the relationship of serum transferrin concentration with history of thrombosis, with adjustment for erythrocytosis versus anemia and iron deficiency determined by model selection (Methods). As shown in Table 3, transferrin was higher in patients without a history of thrombosis (adjusted mean (95% confidence interval (CI)): 324 (306 - 341) mg/dL, compared to 277 (237 - 316) mg/dL in those with such a history and β (95% CI): 47 (8.3 - 86) mg/dL (P = 0.018)). There was also a trend of higher transferrin in the subgroups of patients without a history of venous thrombosis (P = 0.22) or arterial thrombosis (P = 0.044).

Discussion

Persons who move from low to high altitude have an increased risk of thrombosis [13], but it is not known if there is a difference in thrombosis between evolutionarily adapted high-altitude natives, Bolivian Aymaras, born and living at high altitude their entire life, compared to those living at sea level. We examined the relationships of iron deficiency and transferrin with history of thrombosis in Bolivian Aymara highlanders with either anemia or erythrocytosis.

Our findings confirm that iron deficiency is associated with increased serum concentrations of transferrin and with increased history of thrombosis in people living at high altitude. However, our data indicate that increased transferrin level is not part of the mechanism of increased thrombotic risk, and that it may even protect people from thrombosis.

Other reports provide support for our findings including Chuvash erythrocytosis, a congenital disorder causing up-regulated HIFs and high thrombotic risk, wherein increased transferrin is associated with protection from thrombosis [17]. Furthermore, in Chuvash erythrocytosis, an intronic single nucleotide polymorphism (SNP) in *TF*, the gene for transferrin, is associated with higher transferrin levels and further protection from thrombosis [17], which strengthens the potential causal relationship between increased transferrin and a lower risk for thrombosis. In a study from Finland of over 2,000 subjects, higher total iron binding capacity (TIBC), which represents serum transferrin, was associated with decreased risk for acute myocardial infarction, while lower ferritin showed a trend for an increased risk [21]. In a meta-analysis of almost 50,000 subjects, higher serum transferrin was associated with a lower risk of venous thrombosis, but in contrast to our findings, higher serum ferritin was associated with thrombosis [20].

Transferrin elevation is induced by both iron deficiency and hypoxia via HIF signaling [7]. Iron deficiency enhances hypoxic responses by inhibiting the activity of iron- and oxygen-dependent prolyl hydroxylases (PHDs) that hydroxylate

Table 2. Independent Correlations With Serum Transferrin Concentration in 286 High Altitude Patients, 137 With Anemia and 149 With Erythrocytosis

Baseline variable	β (95% CI)	P value	N
Demographics			
High altitude anemia	-26 (-51 - -1.7)	0.037	288
Age (years)	0.13 (-0.67 - 0.94)	0.75	288
Female gender	-9.3 (-34 - 16)	0.47	288
Blood count			
MCV (fL)	-1.38 (-2.26 - -0.496)	0.0024	288
WBC (/µL)	-0.404 (-1.48 - 0.667)	0.46	287
Neutrophils (/µL)	-0.580 (-1.66 - 0.501)	0.29	288
Lymphocytes (/µL)	0.476 (-1.03 - 1.98)	0.54	288
Platelets (× 10^3/µL)	-4.80 (-31.2 - 21.6)	0.72	287
Iron metabolism			
Iron (µg/dL)	-1.94 (-5.77 - 1.88)	0.32	271
Ferritin (ng/mL)	-14.2 (-22.1 - -6.23)	< 0.001	288
Iron deficiency	49 (24 - 73)	< 0.001	288

Serum transferrin was regressed on baseline variables using univariate linear models. WBC, neutrophils, lymphocytes, and iron were square root transformed; platelets and ferritin were logarithm transformed. WBC: white blood cell; MCV: mean corpuscular volume; CI: confidence interval.

HIF-α subunits, permitting their recognition by VHL [6] and subsequent proteasomal degradation. Potential mechanisms for increased thrombosis in iron deficiency that do not involve elevated transferrin include elevated factor VIII [23], increased tissue factor [24], decreased KLF2 [25], chronically increased erythropoietin [17, 26], and thrombocytosis [27]. However, we did not observe a correlation between increased platelet count and history of thrombosis in any of the analyses in this study.

The discrepancy between studies describing transferrin as a risk factor for thrombosis in mice [8, 15, 16] and those describing transferrin as a protection from thrombosis in humans [17, 20, 21] may in part be explained by the fact that $FeCl_3$-mediated induction of thrombosis in mice does not fully reflect thrombogenesis in humans [28].

One of the genes activated by HIF-1 and HIF-2 at high altitude is plasminogen activator inhibitor-1 (*PAI-1*), a regulator of numerous pathophysiological processes including thrombosis. It has been proposed that by inducing the expression of PAI-1, HIF-2 can contribute to thrombosis [29]. Similarly, in an acquired erythrocytosis, polycythemia vera, and in a related disorder, essential thrombocythemia, HIF activity is augmented in neutrophils and platelets and is associated with HIF-1-mediated upregulation of tissue factor and other prothrombotic genes [24, 30]. In these disorders transcription factor KLF2 that inhibits thrombosis is decreased, providing an additional mechanism of a prothrombotic milieu by augmented hypoxia signaling [25]. Here, we report the increased history of thrombosis in environmental hypobaric hypoxia.

In summary, our study of a population of Bolivian Aymaras exposed to environmental hypoxia confirms the association of iron deficiency with history of thrombosis, while raising questions about whether the elegant studies of prothrombotic effects of increased transferrin in mice are applicable to human subjects. In fact, like Chuvash erythrocytosis [17], increased transferrin may protect from thrombosis at high altitude in the Aymara population. Whether these findings can be generalized to non-highlanders or to populations without similar genetic adaptations to hypoxia will require further investigation.

There are several limitations to our study. The incidence of thrombosis was assessed retrospectively by means of chart review. The sample size for the subgroup of patients with a history of arterial thrombosis is relatively small, reducing statisti-

Table 3. Transferrin Concentrations (mg/dL; Median and IQR) According to the History of Thrombosis at High Altitude (Adjusted for Erythrocytosis Versus Anemia and Iron Deficiency)

	Transferrin in subjects with no thrombosis history, adjusted mean (95% CI)	Transferrin in subjects with a history of thrombosis, adjusted mean (95% CI)	β (95% CI)	P value
Total thrombosis	324 (306 - 341) (n = 256)	277 (237 - 316) (n = 30)	-47.2 (-86.0 - -8.32)	0.018
Venous thrombosis[a]	321 (303 - 339) (n = 266)	292 (245 - 339) (n = 20)	-29 (-75.5 - 17.5)	0.22
Arterial thrombosis[a]	321 (304 - 338) (n = 275)	258 (196 - 320) (n = 11)	-63.2 (-124 - -1.96)	0.044

[a]There was one patient with both venous and arterial thrombosis. CI: confidence interval; IQR: interquartile range.

cal power and reliability of the subgroup analyses. We did not measure plasma levels of proteins involved in thrombotic events such as fibrinogen, PAI-1, KLF2 or tissue factor, and this limits the mechanistic insights that we can draw from our findings.

Supplementary Material

Suppl 1. Demographics, laboratory studies, and iron status in high altitude anemia and high altitude erythrocytosis patients.

Suppl 2. Demographics and laboratory variables according to iron deficiency in high altitude anemia and high altitude erythrocytosis patients.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

RA conceived the project, designed the study, supervised and interpreted data, wrote the manuscript, and finalized the submitted manuscript. EM analyzed and interpreted the data. JP helped to interpret the data, provided additional insights, and edited and approved the final manuscript. TG provided critical conceptual and statistical input and edited the manuscript. XZ provided statistical analysis and interpretation and edited the manuscript. DP wrote and edited the manuscript. MC collected the data, helped to interpret the data. VRG helped to write the manuscript, analyzed and interpreted the data, provided additional insights, and edited and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon request.

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