

Research Article

Higher Serum Ferritin in Tibetan and Han Populations with Diabetes Living on the Tibetan Plateau

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Abstract

Objective: Tissue iron has emerged as a significant risk factor for diabetes. Pathways that sense and regulate iron and oxygen interact, but few studies examined the interactions of hypoxia and iron in determining diabetes risk in human populations. Accordingly, metabolic phenotyping with analysis of iron homeostasis in both Tibetan and Han Chinese living at 2300-3900m altitudes were conducted.

Research design and methods: Data were collected on Tibetan and Han Chinese living at intermediate altitudes. Iron homeostatic and metabolic parameters including homeostasis model assessments (HOMA), hemoglobin A1c, serum ferritin and transferrin saturation were determined.

Results: Serum ferritin is higher in both Tibetan groups compared to the respective Han groups, and higher in each diabetic group compared to nondiabetics of the same ethnicity. Serum iron and transferrin saturation were also higher in the Tibetan diabetics than the Tibetan non-diabetics. Serum iron was significantly correlated with ferritin levels in the four combined groups ($r^2=0.07313$, $p<0.05$) and even stronger in the Tibetan diabetic group ($r^2=0.2702$, $p<0.05$). HOMA- β was negatively correlated with ferritin in the Tibetan combined groups ($r^2=0.020$, $p<0.05$), and HOMA-IR tended to be positively correlated with ferritin ($r^2=0.018$, $p<0.05$).

Conclusion: Iron parameters differ both between Han and Tibetans and between diabetics and nondiabetics of both populations. High ferritin, which in these cohorts reflects iron status, is a risk factor for diabetes in both groups, although how iron status relates to the diabetes phenotype differs between the two groups, possibly related to their differing histories of adaptation to high altitude.

Keywords: Iron; Ferritin; Diabetes; Tibetan Adaptation

Key Messages

- The study presents evidence of the relationship between serum ferritin, a measure of tissue iron stores that has been linked to diabetes risk in other populations, and diabetes in Tibetan and Han populations living at altitudes of 2300 m-3900 m.
- The study also presents associations of glucose metabolic phenotypes (homeostasis model assessments, HOMA) in those with diabetes.
- Due to the relatively low prevalence of diabetes in Tibetan populations, the sample size was constrained
- This study is cross-sectional and therefore, future prospective and follow-up studies to reveal the interactions analysis of iron metabolism and diabetes in Tibetans and Han populations are indicated.
- The ethnic background of the subjects is by self-report

Introduction

Many factors contribute to the risk of diabetes, including genetics, ethnicity, altitude, and diet [1]. Tissue iron has emerged as an additional significant risk factor for diabetes and has been shown to play an important role in metabolic regulation [2,3]. The initial association between diabetes risk and iron emerged from studies of heritable

diseases of iron overload such as hereditary hemochromatosis (HH) [4]. More recent studies demonstrate that the relation between iron and diabetes also exists in the general population and across the broad range of "normal" iron, and an associations between iron and diabetes have been established in Caucasians [3,5], persons of African descent [6], and several Asian populations [7-11,12]. The mechanism by which

iron confers diabetes risk, however, is not established in all of these populations, and the interactions of genetics, diet, and geography with the degree of risk are also unknown.

The interaction of iron and altitudes particularly interesting because residence at higher altitudes is inversely associated with diabetes, but hypoxia responsive pathways also increase iron absorption to allow increased erythropoiesis [13]. Tibetans have successfully adapted to reside at altitudes of up to 5000 m [14,15] and it has been reported that there is a reduced prevalence of diabetes and metabolic syndrome in Tibetans [16]. The genetic determinants of that adaptation include changes in the hypoxia sensing pathway [15]. One characterized genetic mechanism, for example, is a gain of function mutation that confers increased oxygen affinity to the proline hydroxylase that would normally be inactivated by hypoxia, thus facilitating stabilization of hypoxia inducible factors [17]. The adaptation was hypothesized to protect Tibetans from the induction of harmful levels of polycythemia. The mutation, which partially disables the hypoxia response, would also be expected to render Tibetans *less* sensitive to induction of the diabetes-protective hypoxia response to altitude. Because the hypoxia sensing pathway exerts major effects on multiple metabolic pathways and senses both tissue iron and oxygen levels [18], it is likely that altitude and iron interact to affect metabolism and diabetes risk, and that these interactions may differ in Tibetans. Interactions between iron and hypoxia have been studied in animal models and shown to affect hepatic glucose production [19], for example, a major factor in diabetes, but their interaction in human populations has not been examined.

In order to begin to address these issues, we have examined metabolic phenotypes and measures of iron homeostasis in Tibetan and Han Chinese with and without diabetes, living at altitudes of 2300-3900 m. The aim of this study was to identify how iron and high altitude hypoxia interact in a population of Tibetan highlanders genetically adapted to high altitude, compared to the non-adapted Han Chinese.

Participants and Methods

Participants

This cross-sectional study included one hundred Tibetan residents of an urban centre (Yushu, 3300-3900m altitude), with and without diabetes, randomly selected from a population receiving routine health screening, at Qinghai University Affiliated Hospital. One hundred Han Chinese individuals, with and without diabetes, matched for age and sex, were selected from a clinic-based population, at the Qinghai University Affiliated Hospital, in Xining (2300m). All the participants were chosen between September 2013 and September 2016.

Data collection and measurement

Clinical characteristics including sex, age, body mass index (BMI), and medical history were recorded. Height and weight were measured according to a standardized protocol and technique, with participants wearing no shoes. BMI was calculated as weight (kg)/height (m²). Blood pressure was measured by trained professionals, using an electronic sphygmomanometer (OMRON HEM-7200), and each participant rested for at least 20 min before measurements were taken.

Health screening included the measurement of fasting glucose and glycated haemoglobin (HbA1c) values. Blood samples were drawn from participants' antecubital veins for measuring fasting blood glucose (FBG), triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels. From this information, de-identified participants of each ethnicity (Tibetan and Han Chinese), with no known history of diabetes and who had not taken any insulin or related drugs, were chosen. From among them, 100 individuals of each ethnicity who were newly diagnosed as having diabetes, based on fasting glucose (≥ 126 mg/dl) or HbA1c ($\geq 6.5\%$) criteria, or who were nondiabetic, were randomly chosen. Individuals with known hematologic disorders, previously diagnosed diabetes, a history of recent (within 1 year) blood transfusion, and malignancy were excluded. In the case of those individuals, the blood samples drawn for health screening were used for the determination of levels of serum insulin and lipids, and iron parameters. The study was approved by the Ethnic Committee of Qinghai University, and the Institutional Review Board of Wake Forest University. Extra clinical samples were used for the additional testing of iron parameters.

Laboratory studies

Fasting blood glucose (FBG), fasting serum insulin, ferritin and serum iron, TG, LDL, HDL, total cholesterol (TH), and HbA1c levels were analysed by latex agglutination immunoassay (DCA 2000 HbA1c, Siemens Healthcare Co Ltd, Munich, Germany). These parameters were measured by standard techniques used in the clinical chemistry laboratories at the Qinghai University Affiliated Hospital. HOMA-IR and β -cell function (HOMA- β) (%) values were calculated as $[FPG \text{ (mg/dl)} \times IRI \text{ (}\mu\text{U/ml)}] / 405$ and $[IRI \text{ (}\mu\text{U/ml)} \times 360] / [FPG \text{ (mg/dl)} - 63]$, respectively.

Iron metabolic parameters were measured using an automated time-resolved immunofluorometric assay (Finland) and the reference values were: Serum iron, Male 11.6–31.7 $\mu\text{mol/L}$; Female 9.0–30.4 $\mu\text{mol/L}$, Total Iron Binding Capacity: 45–66 $\mu\text{mol/L}$, Transferring saturation, Male 20–50%; Female 15–50%, and Serum ferritin, Male 20–240 ng/mL; Female, 10–100 ng/mL

Statistical analysis

Continuous variables that followed a skewed distribution were transformed to normal distribution by natural log or square root transformation. Using a Students' *t*-test or Chi-square, the distribution of clinical and laboratory measurements was tested between individuals with and without diabetes, in the Han Chinese and Tibetan groups, respectively. Pearson and Spearman correlations were used to assess the correlations between ferritin levels, iron concentrations and other variables, in the two groups. Analyses were performed using SPSS 14.0 for Windows software package (SPSS, Chicago, IL). *P* values <0.05 were considered statistically significant.

Results

Characteristics of the Tibetan and Han Chinese study populations

Tibetan residents with diabetes ($n=100$) and Han Chinese with diabetes ($n=100$) were matched to 100 subjects of each group

without diabetes, with respect to age, gender, body mass index, total hemoglobin and blood pressure (Table 1). As expected, each diabetic group had higher fasting glucose values than their respective non-diabetic group. HbA1c was not determined in those with FBG less than 126mg/dL. In the Tibetan diabetes group, surprisingly lower triglyceride levels, and lower HDL and higher LDL were noted compared to the non-diabetic group. LDL cholesterol concentrations were also higher the non-diabetic Han compared to the nondiabetic Tibetans (Table 1).

Iron parameters differ between Han Chinese and Tibetan populations, and between those with and without diabetes, and we identified a unique association between diabetes risk and the iron indices, in Tibetans. Because of our study population, which included Tibetans and Han Chinese individuals, both of whom reside in intermediate altitudes of 2300-3900 m, we examined the interrelations between serum iron-related parameters, ethnicity, and diabetes status, respectively. The ferritin level was higher in the diabetes group compared to the non-diabetes group, within the

same ethnicity ($p < 0.01$, Figure 1A). Our hypothesis is that, in the non-diabetes groups there should no difference in the ferritin level; however, it was observed that the ferritin level was higher in both Tibetan diabetes and non-diabetes groups, compared to the respective Han Chinese groups ($p < 0.01$); this indicates that Tibetan populations showed specialized tissue iron storage.

Next, we assessed both β -cell function and insulin resistance, according to the homeostasis model assessment (HOMA- β and HOMA-IR). Insulin values were only available in the diabetes groups. The HOMA-IR values were greater than 2 in both the diabetes groups (Table 2); this was consistent with insulin resistance [19]. The HOMA-IR and HOMA- β values did not differ between the Han Chinese and Tibetan populations. The HOMA- β value was negatively correlated with ferritin, in both groups ($r^2 = -0.02$, $p = 0.04$), and the HOMA-IR value tended to be positively correlated with ferritin ($r^2 = 0.02$, $p = 0.05$). Within each ethnicity, the same trends held, but did not reach significance in the smaller groups (Table 2).

Table 1 Distribution of variables in Tibetan and Han Chinese populations with and without diabetes. Results are presented as median (interquartile ranges).

Variable	Tibetan		Han Chinese	
	Diabetes group n=100	Non-diabetes group n=100	Diabetes group n=100	Non-diabetes group n=100
Age(years)	50(44~59.75)	50(45~58.75)	52(46~58)	54(48~58)
Gender (male%)	54%	52%	49%	55%
BMI(kg/m ²)	24.08(22.53~26.23)	24.18(21.76~26.5)	24.22(22.2~26.2)	24.15(21.84~25.95)
Haemoglobin (g/L)	160(150~172)	163.02(146.97~172.09)	163(150~172)	160.34(144.49~173.58)
Diastolic Pressure (mmHg)	80(80~88)	80(80~84)	80(76~89)	80(78.25~85.75)
Systolic Pressure(mmHg)	124(120~140)	120(120~130)	120(120~130)	120(119.25~137.25)
Fasting Glucose(mmol/L)	9.36(8~10.94)	4.59(4.3~5)	8.15(6.8~11.39)	4.6(4.3~5.06)
Glycated Haemoglobin (%)	10.25(8.55~11.88)	-	8.8(7.05~10.2)*	-
Triglyceride(mmol/L)	1.68(1.32~2.33)	1.71(1.38~2.35) ^Δ	1.73(1.32~2.32)*	1.76(1.36~2)
Cholesterol(mmol/L)	4.58(4~4.93)	4.57(3.88~5.09)	4.52(3.96~5)	4.26(3.75~5)
HDL(mmol/L)	0.97(0.81~1.13)	1.03(0.85~1.19) ^Δ	1.03(0.88~1.19)*	1.08(0.88~1.26)
LDL(mmol/L)	3.01(2.25~3.63)	2.44(2.03~2.94) ^Δ	2.58(2.1~3.28)*	2.57(2~3)
Iron Metabolism				
Iron(umol/L)	20(16.4~24.9)	15.6(12~20.58) ^Δ	16.9(12.85~22)*	15.75(12.9~18.83)
Ferritin (ng/ml)	613.89(457.07~812.75)	279.85(231.32~359.56) ^Δ	234.66(173.68~325.25)*	78(59.45~98.63) ⁺
TIBC(umol/L)	29.3(23.1~35)	48.6(43.13~57.08) ^Δ	38(33.05~43.55)*	51.65(47.43~57.4) ⁺
TSAT(%)	0.7(0.5~0.98)	0.33(0.25~0.39) ^Δ	0.46(0.31~0.64)*	0.30(0.25~0.35) ⁺

Notes: * for Tibetan diabetes group vs Han Chinese diabetes group with a significant difference of $p < 0.05$; ^Δ for Tibetan diabetes group vs Tibetan non-diabetes group with a significant difference of $p < 0.05$; ⁺ for Tibetan non-diabetes group vs Han Chinese diabetes group with a significant difference of $p < 0.05$

Abbreviations: LDL, low-density lipoprotein; HDL, high-density-lipoprotein; TIBC, total iron binding capacity; TSAT, transferrin saturation

Table 2. Distribution of HOMA values in Tibetan and Han Chinese diabetes groups. Results are presented as median (interquartile ranges)

Variables	Tibetans with diabetes N=100	Han Chinese with diabetes N=100	Z	p
HOMA-IR	29.35(22.25~34)	25.64(17.02~46.79)	-0.293	0.77
HOMA- β	2.35(1.52~4.04)	2.44(1.49~3.59)	-0.684	0.494

Abbreviations: HOMA, homeostasis model assessment; HOMA-IR, homeostasis model assessment insulin resistance

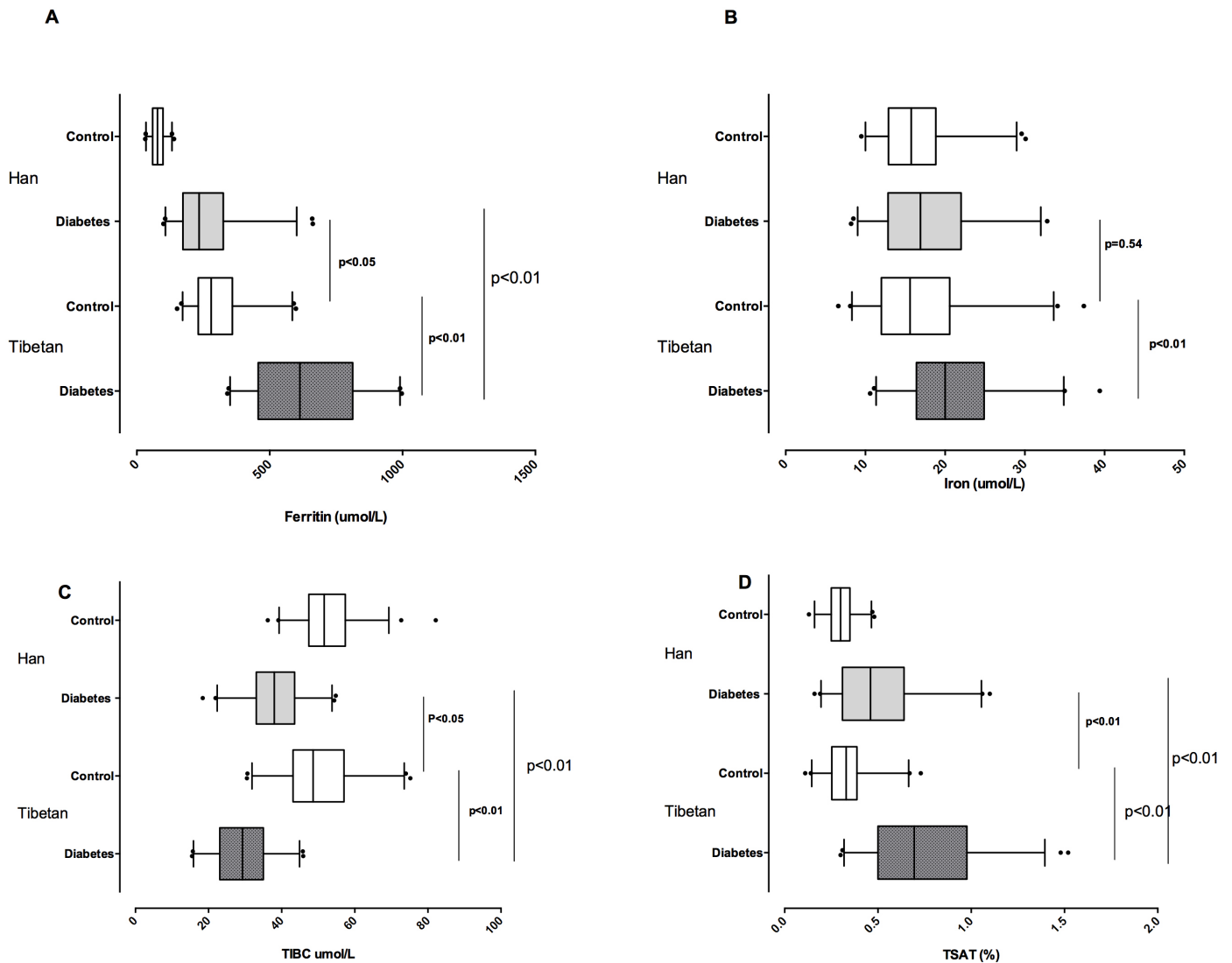


Figure 1. Iron metabolic values in Tibetan and Han Chinese groups with and without diabetes, in terms of A) Serum ferritin level comparisons; B) Serum iron level comparisons; C) Total iron binding capacity comparisons; and D) Transferrin saturation ratio comparisons.

*dot spot indicates the 5-95 percentile of the values.

Serum ferritin reflects the iron status in the study group, while other iron parameters are also associated with diabetes

After, we examined serum iron levels in the four groups. Like in the case of ferritin, the serum iron level was higher in Tibetans with diabetes than Tibetan without it; in addition, it was higher in Tibetan participants with diabetes than Han Chinese participants with diabetes (p<0.01 for both comparisons, Figure 1B), although the trend among Han Chinese participants with diabetes was only higher than those without diabetes in the same population (p<0.05). The same was true of transferrin saturation (p<0.01, Figure 1D). As further evidence that ferritin reflects iron status rather than inflammation, in our study, the serum iron and ferritin levels were significantly correlated in the four groups (r²=0.07, p<0.01, Figure 2). The correlation was even stronger in the Tibetan diabetes group (r²=0.27, p<0.01), but was not significant in the other groups, taken individually.

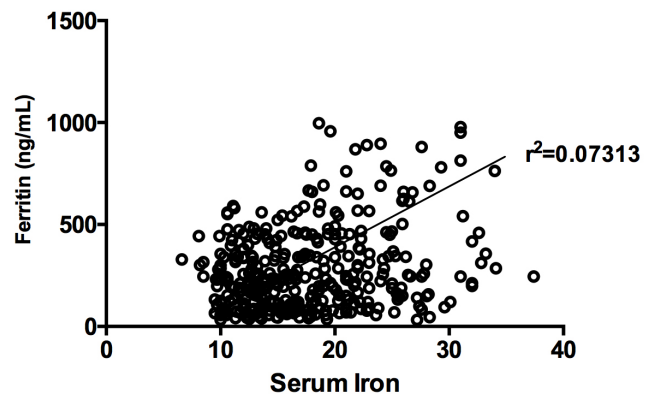


Figure 2. Correlation of serum iron and ferritin levels in Tibetan and Han Chinese populations, with and without diabetes. Scatter-plot diagram.

Higher ferritin levels identified as a new pattern of diabetes risk in Tibetans

Insulin resistance and decreased β -cell function can also result from as well as cause poor plasma glucose stability and hyperglycemia [20]. Therefore, we determined if glucose stability influenced the HOMA- β and HOMA-IR values. The associations of HbA1c levels with the HOMA-IR and HOMA- β values were assessed, respectively. However, HbA1c levels were not found to be correlated with HOMA-IR ($p=0.95$), HOMA- β or ferritin ($p=0.63$), in the Tibetan diabetes group. In the Han Chinese diabetes group, however, HbA1c was significantly negatively correlated with ferritin ($p=0.04$) and the HOMA- β ($p=0.04$) value, and trended toward being negatively correlated with the HOMA-IR ($p=0.11$) value.

Discussion

Iron and diabetes risk in Tibetan and Han Chinese

The connection between iron and diabetes have been the subject of recent reviews [3,4,21-23] and a meta-analysis [24-26]. Originally identified in subjects with hereditary iron overload such as occurs in hereditary hemochromatosis [27,28], the correlation between markers of tissue iron and diabetes has since been noted in numerous populations in the U.S., Europe [3] and elsewhere, including Korean [7], Chinese Han [8-11], African Americans [6,29], and Persian populations [30]. Our findings generally support these studies insofar as Tibetans diabetics have higher ferritin than nondiabetics, and Han diabetics have higher ferritin than Han nondiabetics. However, serum ferritin can rise with systemic inflammation as well as tissue iron, and phlebotomy studies have shown ferritin to be related to tissue iron, but imperfectly so [31]. In general, however, tissue iron, in particular liver iron, is the predominant determinant of serum ferritin levels [32], and ferritin correlates very well with liver iron by imaging criteria [33]. Even in the inflammatory condition of non-alcoholic steatohepatitis, ferritin remains a reliable reporter of tissue iron as assessed by liver biopsy [34]. Further evidence that ferritin is reporting on iron status is the correlation of ferritin with serum iron. Thus, although we do not have direct measures of tissue iron content, the results overall support the finding in multiple populations of a correlation of iron with diabetes prevalence. Further support for this conclusion is the large amount of data from animal and human models that support causal connections between iron and diabetes, mediated both by β -cell failure and insulin resistance with the underlying mechanisms including oxidant stress and modulation of adipokines that affect glycemia [29,31,35], and data from NHANES showing that ferritin reflects dietary iron intake rather than inflammation [5].

Our findings also indicate that ferritin remains associated with diabetes in residents of higher altitudes. This replicates a previously reported association of ferritin with diabetes in Han Chinese living at altitude [36]. Living at higher altitudes has been reported to be associated with lower diabetes risk [35] and likewise activation of hypoxia-sensing pathways has salutary effects on glucose homeostasis [37]. Thus, our study indicates that in both populations the association with iron is not erased by the beneficial effects of altitude, though we do not have diabetes incidence and prevalence data as a function of iron with which to examine their possible interaction.

We also show that Tibetans with and without diabetes have significantly higher ferritin levels and transferrin saturations than the Han population. The reasons for this are not clear. One possibility is diet, with the traditional Tibetan diet including substantial amounts of high-iron barley [1], and red yak meat; dietary surveys were not done in this study but would be useful in future studies aimed at explaining these parameters. Epidemiological investigations are needed to explain if the relative risk of diabetes for a given ferritin level is altered in Tibetans compared to Han. Interestingly, although the transferrin saturation is significantly higher in Tibetans with diabetes, which is accounted as much by low iron binding capacity as by higher serum iron, but the basis for this is not known. Finally, hypoxia also induces increased absorption of dietary iron to support polycythemia at altitude. Tibetans have genetically adapted to high altitude with unique haplotypes and mutations in genes of the hypoxia sensing pathways [13], and this may explain part of the differences between the Tibetans and Han in the current study, who are residing at similar altitudes.

Mechanisms of iron-associated diabetes in the Han and Tibetans

Further indication that the association of ferritin, iron and diabetes risk is complex is that if the relationship were simply one of high iron, and if the high ferritin values in Tibetans did simply reflect high iron, that might imply higher diabetes risk in that population, whereas epidemiologic studies suggest that Tibetans have a lower prevalence to diabetes [9]. A minority of the subjects in this study were overweight, with average BMI in all groups being ~ 24 , consistent with the reported association of altitude with leanness [38], and that might be expected, like the altitude itself [1], to counter any degree of iron-associated risk that might also be present. The associations of ferritin with HOMA- β and HOMA-IR were weaker than observed in the other populations cited in the Introduction, yet similar between Han and Tibetan groups. This, too, may be related to the dilution out of these effects by the altitude. The results suggest that altitude adds a new dimension to reported diabetes risk associations, and that further studies of diabetes prevalence in different populations living at high and low altitudes, with more detailed physiologic phenotyping and genotyping, may shed light on the pathogenesis of this disease.

Conclusions, unanswered questions and implication

To our knowledge, this is the first study to suggest that a special relationship exists between tissue iron storage and diabetes risk, in Tibetan populations. Furthermore, it is suggested that residing in high altitudes may impact the associations between the glucose metabolic phenotypes, and lead to more stabilised glucose levels and higher dependency on glucose for energy. In addition, the new patterns of iron homeostasis in Tibetans with urban lifestyles living at high altitudes might contribute to the special adaptations. Notably, since this study had a cross-sectional study design that involved a review of health record data, it was also impossible to obtain other data that may have been of interest, such as dietary histories, or further laboratory measures of other iron-related measures. Therefore, a future perspective and follow-up study to analyse the interactions of

iron metabolism and diabetes, in Tibetan populations, is required. Most importantly, the genetic background of the study's participants was not identified. In addition, the major regulators of iron such as hepcidin and transferrin were also not investigated, and both factors play emerged effects on iron homeostasis in human beings. The prevention and management of diabetes through dietary iron intake intervention should be a potential therapy target in the future.

Contributors

ZB and DM wrote the manuscript; CZ and JZ collected and supplied the data; SL with YZ, RF and DM analysed the data; SC with RG designed and coordinated the study. All authors reviewed and approved the final manuscript.

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Competing interests: None.

Ethics approval: The Institutional Ethnic Committee of Qinghai University and the Institutional Review Board of Wake Forest University approved the study.

Data sharing statement: The data that support the findings of this study can be obtained from the corresponding author upon reasonable request.

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