The Regulatory Effect of Blood Group on Ferritin Levels in Aging

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Abstract

Background

Ferritin plays a pivotal role in the ageing process. Previous studies have identified statistically significant differences in ferritin levels among various ABO blood groups. However, the interaction between the ABO blood group and ferritin levels during senescence remains underexplored.

Methods

We analyzed data from 3,843 individuals aged 40 and over who underwent blood type

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and ferritin testing at Beijing Zhongguancun Hospital. Spearman correlation analysis was employed to examine the relationship between the non-normally distributed biochemical indicators and ferritin levels. Age was considered the independent variable, while gender and biochemical indicators related to ferritin served as control variables. Blood type was analyzed as a moderating factor to evaluate its impact on the relationship between age and ferritin levels.

Results

Our findings revealed a negative correlation between ferritin and age ($\rho = -0.099$, $p < 0.001$). Significant differences in ferritin levels were observed between genders ($p = 0.005$) and blood groups ($p < 0.001$). The influence of age on ferritin levels varied across different blood groups, particularly in individuals with blood types A ($p = 0.003$, $\beta = -0.072$) and B ($p < 0.001$, $\beta = -0.110$), where the negative association between age and ferritin was more pronounced.

Conclusion

This study confirms that different blood groups exert a significant regulatory effect on the relationship between age and ferritin levels, most notably in blood groups A and B. These results suggest that middle-aged and elderly individuals with blood types A and B may benefit from iron supplementation.

Key words: ferritin levels, ABO blood group, aging, regulatory effect

Introduction

Rapid population ageing has emerged as a significant public health challenge in China and globally, as the deterioration of tissues and organs associated with ageing is a primary contributor to many chronic diseases [1]. This degeneration will be reflected in the fluctuations of physiological indicators, which indirectly reflect the state of health [2]. Consequently, preventive strategies and interventions targeting key physiological indicators that promote healthy ageing are essential.

Among the numerous physiological indicators, ferritin, a key iron storage protein, plays a significant role in various physiological and pathological processes, including

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coronary artery disease, malignancies, sideroblastic anemias, neurodegenerative disorders, and hemophagocytic syndrome [3]. It has been proposed that SF can transport iron into cells, constituting the main pathway of iron supply to oligodendrocytes for myelin production, and then involved in neurotransmitter synthesis in the central nervous system, thus affecting working memory [4]. In later life, reduced iron stores are associated with an increased risk of impaired physical and cognitive capacity, as well as up to a twofold higher risk of mortality [5, 6]. A cross-sectional study of the Kerr Anglican Retirement Village Initiative in the Ageing Health cohort (aged 65-90 years) found that serum ferritin (SF) positively correlates with neocortical amyloid-β load (NAL). The findings suggested that impaired iron mobilization may be an early event in the onset of Alzheimer's disease (AD). Ferritin has the potential to serve as a blood biomarker panel for preclinical AD [7]. In addition, iron plays a crucial role in erythropoiesis, oxygen transport throughout the circulatory system, mitochondrial respiration, and protection against free radicals in high-energy-demand cells, such as cardiomyocytes. Research has demonstrated that serum ferritin levels decline with age, while the prevalence of heart failure (HF) rises. In patients with chronic heart failure, iron deficiency is associated with impaired functional capacity and an increased risk of HF hospitalization and mortality [8]. Therefore, understanding the characteristics of iron levels with age may have significant clinical implications, especially considering the availability of routine blood tests to detect iron deficiency and various therapeutic options for iron repletion.

Recently, an intriguing study revealed that among a total of 7,723 healthy blood donors, individuals with blood type A exhibited lower concentrations of ferritin. In contrast, blood type B was associated with significantly higher levels of ferritin. A statistically significant heterogeneity in ferritin levels among the ABO blood groups was observed ($p < 0.001$) [9]. As we know, ABO blood groups are ABO antigens (i.e., A, B, AB, and O), which are glycoproteins and glycolipids expressed by the ABO gene on the surface of red blood cells, as well as a variety of human cells and tissues. Therefore, the clinical significance of ABO blood type extends beyond transfusion medicine and solid organ

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or hematopoietic transplantation. These antigens may also participate in the pathogenesis of various systemic diseases, including cancer, diabetes, infectious disorders, and cardiovascular disease [10]. Therefore, the vast majority of studies have limited their investigation of this intriguing relationship to cohorts of high-risk patients, resulting in a scarcity of evidence regarding the physiological influence of ABO antigens on baseline levels of hematological and metabolic parameters. Given the changes in iron levels with age and the potential impact of blood type on these levels, it remains unclear whether blood type exerts a regulatory effect on iron levels in healthy ageing populations (**Figure 1**). To explore this ambiguous association, we conducted a study within the Beijing Health Examination Cohort (BHEC) to examine the influence of different blood types on ferritin levels in ageing individuals, with the aim of guiding personalized clinical treatment in the future.

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Materials & Methods

Study Design and Participants

The biochemical examination data were collected from 3,843 individuals aged 40 and above who underwent blood type and ferritin testing at Beijing Zhongguancun Hospital between July 2019 and July 2024. A total of 883 middle-aged and elderly individuals with missing a large number of examination data were excluded from the study. Ultimately, 2,960 healthy participants were included in this retrospective study. The Ethics Committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, approved the study protocol (ZS2024001). The study was conducted in accordance with the Declaration of Helsinki and its amendments. All participants provided written informed consent prior to enrollment. Clinical trial number: not applicable.

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Measures

Age, sex, self-reported health status, and medical history were recorded. Blood samples were obtained under fasting conditions and analyzed within 2 hours of centrifugation. The blood chemistry studied was assessed by standard automated techniques, including

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Architect C 8000 auto-analyzer and Axsyme Third-Generation Immunoassay System (Abbott, IL). This analysis included indicators of liver function, glycometabolism, lipid metabolism, myocardial function, thyroid function, and inflammatory factors (**Supplementary Table 1**).

Statistical analysis

Descriptive statistics and Spearman correlation analysis were conducted using SPSS version 27.0. Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage). Then, the normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney test was employed to compare the normal distribution between the two gender groups. The Kruskal-Wallis test was utilized to compare median differences among multiple blood type groups. Spearman correlation analysis was performed to evaluate the relationship between biochemical indices and ferritin levels. Finally, age was treated as the independent variable, with gender and biochemical indicators associated with ferritin serving as control variables. Blood type was analyzed as a moderating variable to determine its effect on the relationship between age and ferritin levels. P-values less than 0.05 were considered statistically significant.

Results

Descriptive Statistical Analysis of Each Biochemical Index

We collected biochemical examination data from 3,843 individuals aged 40 and above who underwent health check-ups at Beijing Zhongguancun Hospital. A total of 2,960 healthy participants, with an average age of 53.96 ± 12.19 years, were included in this study, of which 900 (30.41%) were male. Among these participants, 859 (29.02%) had blood type O, 831 (28.07%) had type A, 978 (33.04%) had type B, and 292 (9.86%) had type AB (**Table 1**). There were individual differences in various biochemical indices, particularly in liver and kidney function, metabolic function, and myocardial damage. Notably, the mean ferritin level was 288.16, with a standard deviation of 99.89,

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indicating significant variability in ferritin levels among individuals. However, the median values of all indicators were close to the mean (**Table 1**), suggesting that the distribution of these indicators is relatively concentrated and suitable for further correlation and regression analyses.

Correlation and Univariate Analysis of Ferritin and Other Indicators

Since all variables did not conform to a normal distribution ($p<0.05$) (**Supplementary Table 2**). Spearman correlation analysis was employed for continuous variables, while a non-parametric test was utilized for categorical variables.

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The results indicated a negative correlation between ferritin levels and age ($\rho = -0.099$, $p < 0.001$), suggesting that ferritin levels tend to decrease as age increases (**Table 2**). Additionally, the difference in ferritin levels between men and women was statistically significant ($p = 0.005$) (**Table 3**), highlighting a notable disparity in ferritin levels between the sexes. Furthermore, there were statistically significant differences in ferritin levels across various blood groups ($p < 0.001$) (**Table 4**).

Alanine aminotransferase (ALT) ($\rho = 0.078$, $p < 0.001$), aspartate aminotransferase (AST) ($\rho = 0.039$, $p < 0.05$), γ-glutamyl transpeptidase (γ-GT) ($\rho = 0.074$, $p < 0.001$), creatinine (Cr) ($\rho = 0.105$, $p < 0.001$), alkaline phosphatase (ALP) ($\rho = 0.113$, $p < 0.001$), and lipoprotein(a) (LP(a)) ($\rho = 0.059$, $p < 0.01$) demonstrated significant positive correlations with ferritin (**Table 2**). This suggests that abnormalities in liver, bile, and renal function are associated with increased ferritin levels.

There was a significant negative correlation between apolipoprotein A1 (APOA1) and ferritin ($\rho = -0.086$, $p < 0.001$) (**Table 2**), suggesting that an increase in ferritin levels is associated with a decrease in high-density lipoprotein (HDL) metabolism.

There were significant positive correlations between ferritin and creatine kinase (CK) ($\rho = 0.156$, $p < 0.001$), lactate dehydrogenase (LDH) ($\rho = 0.224$, $p < 0.001$), and myoglobin (Mb) ($\rho = 0.207$, $p < 0.001$) (**Table 2**). These findings suggested that elevated ferritin levels may be closely associated with myocardial injury.

Thyroid-stimulating hormone (TSH) (ρ = 0.126, $p < 0.001$) exhibited a positive correlation with ferritin, whereas free triiodothyronine (FT3) (ρ = -0.174, $p < 0.001$) and total triiodothyronine (TT3) (ρ = -0.168, $p < 0.001$) demonstrated negative correlations with ferritin (**Table 2**). These findings suggested a relationship between thyroid function and ferritin levels.

Interleukin-6 (IL-6) (ρ = 0.103, $p < 0.001$) exhibited a positive correlation with ferritin (**Table 2**), suggesting that ferritin levels are closely associated with the elevation of inflammatory factors.

Glucose (Glu) (ρ = 0.042, $p < 0.05$) and small and dense low-density lipoprotein cholesterol (sd LDL-C) (ρ = 0.038, $p < 0.05$) exhibited a weak positive correlation with ferritin (**Table 2**). This finding suggests that metabolic disorders may be associated with ferritin levels.

The Regulatory Effect of Blood Group on Ferritin Levels with Aging

We included indicators related to ferritin and analyzed the regulatory effects with age as the independent variable, gender and other biochemical indicators as control variables, and blood type as the moderating variable.

In Model 1, which analyzed the direct effects of age and several control variables (including gender, ALT, AST, creatinine, glucose, etc.) on ferritin levels, age exhibited a significant negative effect on ferritin levels ($t = -2.340$, $p = 0.019$). Specifically, as age increased, ferritin levels decreased significantly (**Table 5**). These results indicate that age is an independent factor influencing ferritin levels.

Model 2 incorporates blood type as a regulatory variable based on Model 1 to investigate whether different blood types influence the relationship between age and ferritin levels. The results indicated that blood group B ($p = 0.042$) and blood group AB ($p = 0.048$) had significant effects on ferritin levels compared to blood group O, while blood group A did not show a significant difference (**Table 5**). This suggests that blood groups B and AB may modulate the effect of age on ferritin levels to some extent.

Model 3 further incorporated the interaction term of age and blood type to elucidate the

specific regulatory effects of different blood types on the relationship between age and ferritin levels. The results indicated that various blood groups indeed play a significant regulatory role in this relationship. In blood group A ($p=0.003$, $\beta=-0.072$) and blood group B ($p<0.001$, $\beta=-0.110$), the negative impact of age on ferritin levels was more pronounced, demonstrating a stronger regulatory effect compared to other blood groups. In populations with blood group AB ($p=0.033$, $\beta=-0.044$), the negative effect of age on ferritin was greater than that observed in blood group O, although the regulatory effect was relatively weak (**Table 5**).

Discussion

Ferritin is a vital protein complex responsible for storing excess cellular iron and plays a crucial role in various metabolic pathways, inflammatory processes, stress responses, and the pathogenesis of cancer and neurodegenerative diseases [11, 12]. In recent years, ferritin has been shown to play a central role in senescence, driving the senescence-associated secretory phenotype (SASP) through the induction of senescence and iron accumulation in senescent cells [13]. A cohort study found that both low and high serum ferritin levels were associated with an increased risk of incident heart failure in the general population [14]. A meta-analysis of 11 studies revealed that serum ferritin levels were higher in patients with non-alcoholic fatty liver disease (NAFLD) compared to healthy individuals and were associated with the risk of developing NAFLD [15]. A longitudinal study involving 6,497 participants found that serum ferritin levels were positively and independently associated with the incidence of type 2 diabetes (T2D) and cerebrovascular disease (CEVD) [16]. In our study, we observed a significant correlation between ferritin levels and age, liver function, lipid metabolism, myocardial function, and other biochemical indicators, further suggesting the important role of ferritin in senescence and senescence-associated diseases (**Table 2**). Therefore, ferritin holds promise as a potential predictive biomarker for senescence-associated diseases.

The ABO blood groups have been associated with a variety of health conditions over

the years. A genome-wide association study reported a significant correlation between the ABO locus and ferritin levels [17]. An epidemiological study involving 30,595 participants from the Danish Blood Donor Study indicated that non-O blood group donors exhibited lower ferritin levels compared to those with blood group O [18]. However, the interaction between ABO blood groups and ferritin levels during senescence has not been fully elucidated. Our results suggested that the impact of age on ferritin levels varies significantly among different blood groups for the first time, particularly in individuals with blood groups A and B, where the negative correlation between age and ferritin levels is more pronounced (**Table 5**). It is recommended that middle-aged and elderly individuals with blood groups A and B consider iron supplementation.

Strength and limitation

The strength of this study lies in its analysis of the regulatory effect of blood groups on ferritin levels in middle-aged and elderly individuals as a cohesive group. This approach helps to mitigate the loss of continuity associated with ageing that can occur when dividing participants into distinct age groups. Consequently, both the independent and dependent variables in this study are treated as continuous variables.

Our study has several limitations. First, the cross-sectional analysis of the data does not permit a causal assessment of the relationship under investigation. Second, while we have accounted for some confounding factors, our study lacks data on diet and lifestyle, which may influence ferritin levels. Third, although we included and analyzed some relevant biochemical indicators as control variables, the study did not comprehensively cover all biochemical indicators, and the results may be affected by other unmeasured biochemical factors. Therefore, we plan to incorporate questionnaires and follow-up assessments, as well as include additional biochemical indicators, to enhance the comprehensiveness and rigor of the study in the future.

Conclusions

The ABO blood group appears to influence ferritin levels during ageing, particularly in

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individuals with blood groups A and B. In these groups, the negative correlation between age and ferritin levels is more pronounced among middle-aged and elderly individuals. The mechanisms by which ABO blood groups affect serum ferritin levels in senescence require further investigation.

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Ethics approval and consent to participate

The Ethics Committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, approved the study protocol (ZS2024001). The study was conducted in accordance with the Declaration of Helsinki and its amendments. All participants provided written informed consent prior to enrollment. Clinical trial number: not applicable.

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Consent for publication

All the works involved in the paper are original. It has neither been published elsewhere, nor is it currently under consideration for publication elsewhere.

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Availability of data and material

The data has not been previously presented orally or in poster format at scientific meetings. If you would like to request the data for non-profit scientific research, please contact the corresponding author.

Competing Interests

All authors declare that they have no actual or potential conflicts interest.

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Authors' Contributions

XL. N. and MK. P. were responsible for the organization and develop the trial design, final approve the version to be published. XL. N. was the chief investigators and responsible for the data analysis. FH. Y. was responsible for collecting and interpreting data, and verifying results. All authors contributed to the writing of the final manuscript.

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Figure legends:

Figure 1. Schematic diagram of this study design.

Tables:

Table 1. The characteristics of all variables

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Variable	N	Mean/(n, %)	Standard deviation	Median
Age	2960	53.959	12.185	51.000
Gender	2960	Male (n=900, 30.41%) Female (n=2060, 69.59%)		
Blood group	2960	A (n=831, 28.07%) B (n=978, 33.04%) O (n=859, 29.02%) AB (n=292, 9.86%)		
Fer	2960	288.162	99.894	303.210
ALT	2960	22.262	16.081	19.000
AST	2960	22.375	13.315	20.300
ALP	2960	73.943	25.553	82.510
Cr	2960	68.404	22.250	65.000
GGT	2960	30.733	28.747	22.000
GLOB	2960	26.969	3.153	27.010
A/G_A/G	2960	1.575	0.195	1.550
Glu	2960	5.321	0.732	5.290
sd LDL-C	2960	0.848	0.284	0.849
LDL-C	2960	2.892	0.410	2.900
HDL-C	2960	1.233	0.166	1.230
Lpa	2960	205.518	117.043	224.090
APOA1	2960	1.319	0.194	1.290
LDH	2960	234.456	41.973	253.960
LDH-1	2960	40.484	6.914	43.590
CK	2960	112.398	38.566	119.700
CK-MB	2960	15.736	4.454	17.560
α-HBDH	2960	168.106	25.968	178.310

NT-pro BNP	2960	1157.057	532.537	1316.280
TnT	2960	0.045	0.031	0.050
Mb	2960	91.523	57.111	100.490
TSH	2960	2.647	0.753	2.750
FT3	2960	4.301	0.385	4.240
T3	2960	1.510	0.158	1.490
FT4	2960	15.849	1.101	15.860
IL-6	2960	76.228	20.823	81.630

388 Note: N/n, number

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Table 2. Spearman correlation analysis between continuous variables and ferritin

Variables	Correlation coefficient
Age	-0.099***
ALT	0.078***
AST	0.039*
ALP	0.113***
Cr	0.105***
GGT	0.074***
GLOB	0.026
A/G_A/G	-0.035
Glu	0.042*
LDL-C	0.017
HDL-C	-0.067***
sd LDL-C	0.038*
Lpa	0.059**

APOA1	-0.086***
LDH	0.224***
LDH-1	0.221***
CK	0.156***
CK-MB	0.210***
α-HBDH	0.195***
NT-pro BNP	0.189***
TnT	0.209***
Mb	0.207***
TSH	0.126***
FT3	-0.174***
T3	-0.168***
FT4	0.027
IL-6	0.103***

Note: * p<0.05, ** p<0.01, *** p<0.001

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Table 3. Univariate analysis of categorical variables (gender)

Gender	Median (P25, P75)		MannWhitney test Statistic U value	MannWhitney test Statistic z value	p-value
	Male (n=900)	Female (n=2060)			
Fer	301.520 (300.4, 303.6)	302.210 (301.3, 305.4)	869207.500	-2.786	0.005

Table 4. Univariate analysis of categorical variables (blood group)

Blood type	Median (P25, P75)				Kruskal-Wallis test Statistic H value	p-value
	O (n=859)	A (n=831)	B (n=978)	AB (n=292)		
Fer	303.050 (302.5, 303.8)	303.080 (302.5, 303.7)	305.070 (3042.5, 305.7)	306.040 (306.4, 307.6)	24.780	<0.001

Table 5. The regulatory effect of blood group on the level of ferritin with aging

	Model 1	Model 2	Model 3

	B	Standard Error	t	p-value	β	B	Standard Error	t	p-value	β	B	Standard Error	t	p-value	β
Age	-0.384	0.164	-2.34	0.019	-0.047	-0.389	0.164	-2.375	0.018	-0.048	-0.437	0.218	-2.004	0.048	-0.045
Blood type O								-							
Blood type A						-4.872	4.652	-1.047	0.295	-0.022	-4.758	4.640	-1.026	0.305	-0.021
Blood type B						-9.069	4.467	-2.03	0.042	-0.043	-9.058	4.455	-2.033	0.042	-0.043
Blood type AB						-12.768	6.462	-1.976	0.048	-0.038	-12.65	6.444	-1.963	0.050	-0.038
Age*Blood type A											-1.143	0.388	-2.943	0.003	-0.072
Age*Blood type B											-1.552	0.365	-4.248	p<0.001	-0.110

Age*Blood type AB											-1.102	0.517	-2.132	0.033	-0.044
Constant	467.502	34.066	13.724	p<0.001	-	471.505	34.107	13.824	p<0.001	-	466.88	34.065	13.706	p<0.001	-
Control variable			yes					yes					yes		
R^2			0.101					0.103					0.109		
Adjust R^2			0.094					0.095					0.100		
F value			*F* (24, 2935)=13.781, *p*<0.001					*F* (27, 2932)=12.482, *p*<0.001					*F* (30, 2929)=11.929, *p*<0.001		