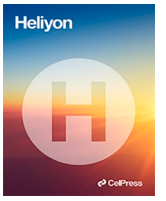
Heliyon 10 (2024) e27898

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Serum ferritin is associated with the presence of ischemic stroke among individuals with type 2 diabetes

Youyou Zhang [a,*], Hui Wang [a], Ruirui Jia [a], Dong Chen [b], Zhaoyang Li [c]

[a] *Department of Geriatric Neurology, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 Xi'wu Road, Xi'an, 710004, Shaanxi, China*

[b] *Department of Clinical Laboratory, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 Xi'wu Road, Xi'an, 710004, Shaanxi, China*

[c] *Department of Occupational and Environmental Health, School of Public Health, Xi'an Jiaotong University, No. 76 West Yanta Road, Xi'an, 710061, Shaanxi, China*

ARTICLE INFO

Keywords:
Serum ferritin
Ischemic stroke
Type 2 diabetes mellitus

ABSTRACT

Background: Epidemiological evidence regarding the possible link between serum ferritin (SF) level and ischemic stroke risk among individuals with type 2 diabetes mellitus (T2DM) is sparse.
Aim: To evaluate the association between SF level in plasma and ischemic stroke risk among individuals with T2DM.
Methods: SF levels were measured in 210 T2DM patients with (n = 165) or without ischemic stroke (n = 45). Multivariate logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).
Results: The SF level of T2DM patients with ischemic stroke was significantly higher than that of patients without ischemic stroke (P = 0.003). The multivariate logistic regression analyses revealed that each 1-SD increase in SF (OR: 1.92; 95%CI: 1.22, 3.03) was significantly associated with increased ischemic stroke risk among T2DM patients. In addition, interaction effect of SF and BMI on ischemic stroke risk were also observed ($P_{\text{for interaction}}$ = 0.037).
Conclusions: Higher levels of SF were independently associated with increased risk of ischemic stroke among individuals with T2DM.

1. Introduction

Diabetes, as a global health problem, has been spreading continuously in the world in recent years. About 578 million people are expected to suffer from this disease in 2030, and the number will continue to rise to 700 million by 2045 [1]. This is most concerning because the prevalence of other diseases, such as stroke, will increase correspondingly with the increase of diabetes, leading to heavier diseases and financial burden. It is reported that patients with type 2 diabetes mellitus (T2DM) have a 2.5-times increased risk of ischemic stroke and a 1.5-times increased risk of hemorrhagic stroke [2]. In addition, stroke accounts for approximately 20% of deaths in individuals with diabetes [3]. In China, the prevalence and incidence of stroke are still rising in the past decade, which is contrary to the trend of many other countries in the world [4,5]. Given that diabetes is a well-recognized independent risk factor for stroke, it is critical to identify biomarkers that can predict the occurrence of stroke among individuals with T2DM.

* Corresponding author.
E-mail address: tjf1289@126.com (Y. Zhang).

https://doi.org/10.1016/j.heliyon.2024.e27898
Received 6 September 2023; Received in revised form 3 March 2024; Accepted 7 March 2024
Available online 8 March 2024

Iron, as an essential metal for living organism, is crucial for the maintenance of cell homeostasis and preservation of life, which display important structural regulatory and catalytic functions in different types of proteins like enzymes, receptors and transporters [6]. Serum ferritin (SF), which is composed of 24 subunits of two types named heavy and light chains [7], is widely used as an indicator of body iron stores in clinical medicine [8,9]. Epidemiological studies have demonstrated the positive association between SF levels trace element status and the development of diabetes [10] and one meta-analysis [11] based on 52 studies indicated that the ferritin levels in T2DM patients were significantly higher than the healthy controls. And studies has also suggested that iron overload associated with the initiate of macrovascular and microvascular complications among diabetes patients [12,13] and iron chelating drugs could be used to control diabetes and diabetic complications [14]. Elevated level of SF is closely related to iron overload [9] and studies have showed that iron overload produces elevated levels of SF [10]. SF is not only a scavenger of free iron, but also a supplier of free iron which can generate oxidative stress [6] and is a source of hydroxyl radicals [8]. It is worth noting that, recent clinical studies have shown that iron-dependent oxidative stress can lead to necrosis and further neurological deterioration following ischemic stroke [15]. The above evidence leads us to speculate the potential association between SF level and stroke prevalence among T2DM patients. Still, the relationship between SF and ischemic stroke in patients with T2DM is poorly documented.

In this study, we aim to investigate the relationship between SF and ischemic stroke prevalence in patients with T2DM and to explore whether SF can be served as independent biomarker to diabetic ischemic stroke in addition to other clinical and laboratory parameters.

2. Methods

2.1. Study population and design

All patients admitted to department of geriatric neurology, the second affiliated hospital of Xi'an Jiaotong University. between May 2021 and March 2022 with T2DM defined by self-reported history of diabetes and treatment with antidiabetic medications or fasting plasma glucose levels of at least 7.0 mmol/L or OGTT 2hBG (2 h blood glucose) $\geq$ 11.1 mmol/L were eligible for present study. Patients with a history of either acute or chronic inflammatory or infectious diseases, chronic liver diseases, chronic kidney diseases, cardiogenic cerebral embolism and severe heart failure, neoplastic diseases and without serum ferritin data were excluded. Finally, a total 210 T2DM patients were included in the analysis in which 165 patients were with ischemic stroke while 45 patients without ischemic stroke which assessed by the magnetic resonance imaging (MRI) brain scans.

The data are anonymous, and the requirement for informed consent was therefore waived. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval No. 2022200).

2.2. Laboratory parameters

The venous blood was collected in all patients after fasting for at least 6–8 h. Early in the morning of the following day, the venous blood was collected and placed in anticoagulant centrifuge tube (4 ml) and EDTA anticoagulant tube (2 ml) respectively. The levels of serum ferritin (SF) were detected using a Cobas 8000 automatic biochemical analyzer, the levels of fasting blood glucose (FBG) and serum lipids including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) were detected using a Beckman AU5800 automatic biochemical analyzer, the levels of hemoglobin A1C (HbA1C) were detected using a BIO-RAD D-100 glycated hemoglobin analyzer, and the blood cell counts including white blood cells (WBC), neutrophil counts, lymphocyte counts, monocyte counts, neutrophil ratios, lymphocyte ratios, monocyte ratios were detected using a Sysmex XN9000 automated hematology analyzer.

2.3. Assessment of covariates

Information of socio-demographic factors (age and gender), lifestyle (smoking and alcohol status), and vascular risk factors were recorded. Smoking or drinking status was categorized into current, former, and never smoking or drinking groups, both current and former are considered to have smoking and drinking risk factors. Patients were considered smokers if they smoked on average more than 10 cigarettes per day for at least 1 year, and patients were considered drinkers if their average daily intake of ethanol was $\geq$30 mL for more than 1 years. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg after repeated measurement or the use of hypotensive drugs. Coronary heart disease (CHD) was defined as a self-reported history of coronary heart disease. The levels of FBG, HbA1C and serum lipids including TC, TG, HDL-c and LDL-c were collected on the basis of biochemical tests.

In addition, blood cell counts (WBC, neutrophil counts, lymphocyte counts, monocyte counts, neutrophil ratios, lymphocyte ratios, monocyte ratios), were also collected on the basis of biochemical tests. And the NLR was calculated as neutrophil counts/lymphocyte counts, LMR was calculated as lymphocyte counts/monocyte counts.

2.4. Statistical analyses

We compared the continuous variables and categorical variables of clinical and biochemical characteristics, and the *t*-tests or Mann-Whitney *U* was used for between-group comparisons of continuous variables and the chi-square tests for categorical variables. Spearman correlation analyses were used to explore correlations between SF concentrations and the inflammation indices.

Multivariate logistic regression analyses were used to estimate the odds ratios (ORs) for SF after adjusting for other clinical and biochemical variables. In addition, subjects were further stratified by BMI (<24.0 or ≥ 24.0 kg/m^2) and the *P* values for the product terms between continuous SF levels and the BMI were used to estimate the significance of interactions.

Statistical analyses were performed using the SPSS 19.0 for Windows software package (SPSS, Chicago, IL). *P* values < 0.05 were considered statistically significant.

3. Results

Table 1 displayed the results of demographic data, glucose levels and vascular risk factors in all participants. No significant differences were observed for the age, gender and BMI between the two groups (all $P > 0.05$). Compared to the T2DM patients without ischemic stroke, the T2DM patients with ischemic stroke possessed higher levels of HAb1C but with no statistics difference ($P = 0.181$). The traditional risk factors including smoking, drinking, hypertension, CHD, and blood lipid components between the two groups had no statistical difference (all $P > 0.05$).

Table 2 showed the results of SF and Inflammation indices from blood cell counts in all participants. T2DM patients with ischemic stroke tend to have higher levels of SF ($P = 0.003$). Meanwhile, in general, compared with those without ischemic stroke, most of the inflammatory indicators showed relatively high levels in those with ischemic stroke except for LMR and the differences of the above indicators did not reach a significant level (all $P > 0.05$).

Spearman correlation analyses (Table 3) showed that SF levels was significantly negatively correlated with lymphocyte counts ($r = -0.204$, $P = 0.009$), lymphocyte ratios ($r = -0.180$, $P = 0.020$), and LMR ($r = -0.197$, $P = 0.011$), while it was significantly positively correlated with neutrophil ratios ($r = 0.178$, $P = 0.022$) among the T2DM population with ischemic stroke.

The multivariate logistic regression analyses (Table 4) revealed that each 1-SD increase in SF (OR: 1.92; 95%CI: 1.22, 3.03) was significantly associated with increased ischemic stroke risk among T2DM patients. Meanwhile, compared with the lowest tertile of SF, the multivariable-adjusted ORs (95%CIs) of ischemic stroke in the highest tertile was 3.65 (1.33, 9.99) for SF. Subgroup analyses (shown in Fig. 1) indicated that the positive association between SF level and ischemic stroke risk was more pronounced among subjects with lower levels of BMI (*P* for interaction = 0.037).

4. Discussion

In our present study, we found the significant positive association between SF and risk of ischemic stroke among individuals with T2DM. Meanwhile, a significant interaction between SF and BMI on ischemic stroke risk was also observed.

In recent years, many evidences indicate that iron is a risk factor in the development of ischemic stroke [8,16] and in vivo studies showed that iron-overloaded animals are more affected by permanent middle cerebral artery occlusion [17]. Ferritin is the major form of stored iron in the brain [18,19], and ferritin-bound ferric iron is released after being reduced to ferrous iron under hypoxic conditions that accompany ischemic stroke, then lead to the disturbances in iron homeostasis [18]. The findings of one prospective study among postmenopausal women conducted by van der A Daphne L et al. showed that higher serum ferritin concentrations in postmenopausal women are associated with an increased risk of ischemic stroke [20]. In vivo studies indicated that the level of ferritin was increased in the cerebral cortex, hippocampus, and corpus striatum in the ischemic brain of the rats [21,22]. Besides, iron disorder with elevated SF levels was also found in patients with T2DM and the association of elevated SF levels with insulin resistance and impaired

Table 1
Basic characteristics of study population.

	T2DM with stroke (n = 165)	T2DM without stroke (n = 45)	*P**
Age (years)	65.54 ± 9.27	64.91 ± 8.48	0.902
Gender (man, %)	71.5	66.7	0.581
BMI (kg/m^2)	24.79 ± 2.88	24.86 ± 2.93	0.547
Smoking (%)	40	37.8	0.864
Drinking (%)	20.6	22.2	0.837
SBP (mmHg)	141.75 ± 22.08	139.47 ± 20.01	0.531
DBP (mmHg)	81.77 ± 12.59	81.13 ± 11.30	0.759
Hypertension (yes, %)	80.6	75.6	0.532
CHD (yes, %)	9.1	6.7	0.769
TC (mmol/L)	4.08 ± 1.22	4.26 ± 1.13	0.398
TG (mmol/L)	1.67 ± 0.88	1.76 ± 1.04	0.564
HDL-c (mmol/L)	1.08 ± 0.25	1.10 ± 0.23	0.694
LDL-c (mmol/L)	2.61 ± 0.92	2.75 ± 0.88	0.367
FBG (mmol/L)	7.39 ± 2.48	7.58 ± 2.72	0.665
HbA1C (%)	7.53 ± 1.52	7.20 ± 1.31	0.181

Abbreviations: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; TG: triglyceride; TC: total cholesterol; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; FBG: fasting blood glucose; HbA1C: hemoglobin A1C.

*: *P* value were derived from Student's t-test or Mann-Whitney *U* test for continuous variables according to the data distribution, and Chi-square test for the category variables.

Table 2
Serum ferritin and inflammation indices levels of study population.

	T2DM with stroke (n = 165)	T2DM without stroke (n = 45)	*P**
SF (ng/ml)	213.89 ± 154.10	152.58 ± 108.09	0.003
WBC (× 10^9/L)	6.61 ± 1.89	6.11 ± 1.63	0.111
Neutrophil counts (× 10^9/L)	4.23 ± 1.71	3.96 ± 1.35	0.320
Lymphocyte counts (× 10^9/L)	1.77 ± 0.64	1.62 ± 0.49	0.148
Monocyte counts (× 10^9/L)	0.46 ± 0.31	0.39 ± 0.16	0.117
Neutrophil ratios (%)	62.73 ± 10.41	63.81 ± 8.10	0.460
Lymphocyte ratios (%)	27.80 ± 9.62	27.02 ± 6.78	0.536
Monocyte ratios (%)	6.77 ± 1.80	6.43 ± 2.20	0.345
NLR	2.80 ± 1.78	2.67 ± 1.52	0.661
LMR	4.27 ± 1.70	4.61 ± 1.89	0.248

Abbreviations: SF: serum ferritin; WBC: white blood cell count; NLR:neutrophil counts/lymphocyte counts; LMR:lymphocyte counts/monocyte counts.
*: *P* value were derived from Student's t-test or Mann-Whitney *U* test for continuous variables according to the data distribution.

Table 3
Spearman correlation between SF levels and the inflammation indices.

Inflammation indices	T2DM without stroke	T2DM with stroke	All participants
WBC (× 10^9/L)	r = 0.05, *P* = 0.746	r = 0.001, *P* = 0.986	r = 0.021, *P* = 0.758
Neutrophil counts (× 10^9/L)	r = 0.005, *P* = 0.977	r = 0.063, *P* = 0.419	r = 0.059, *P* = 0.393
Lymphocyte counts (× 10^9/L)	r = 0.104, *P* = 0.495	r = −0.204, *P* = 0.009	r = −0.137, *P* = 0.047
Monocyte counts (× 10^9/L)	r = −0.097, *P* = 0.527	r = 0.068, *P* = 0.383	r = 0.053, *P* = 0.445
Neutrophil ratios (%)	r = −0.029, *P* = 0.850	r = 0.178, *P* = 0.022	r = 0.134, *P* = 0.052
Lymphocyte ratios (%)	r = 0.112, *P* = 0.464	r = −0.180, *P* = 0.020	r = −0.130, *P* = 0.060
NLR	r = 0.120, *P* = 0.432	r = 0.135, *P* = 0.084	r = 0.126, *P* = 0.069
LMR	r = −0.027, *P* = 0.858	r = −0.197, *P* = 0.011	r = −0.172, *P* = 0.013

Abbreviations: NLR:neutrophil counts/lymphocyte counts; LMR:lymphocyte counts/monocyte counts.

Table 4
Association of serum ferritin with ischemic stroke among individuals with type 2 diabetes.

			SF (ng/ml)			
	OR(95%) for per-SD	***P***	**Tertile 1**	**Tertile 2**	**Tertile 3**	***P* trend***
Model 1	1.76 (1.14, 2.71)	0.01	ref	0.96 (0.42, 1.98)	2.89 (1.15, 7.29)	0.015
Model 2	1.85 (1.18, 2.90)	0.007	ref	1.01 (0.45, 2.27)	3.19 (1.22, 8.36)	0.012
Model 3	1.92 (1.22, 3.03)	0.007	ref	1.01 (0.44, 2.34)	3.65 (1.33, 9.99)	0.007

Model1:adjusted for age, gender and BMI.
Model2: further adjusted for smoke, drink, hypertension, CHD, TC, TG, HDL, LDL, and FBG.
Model3: further adjusted for lymphocyte counts, neutrophil ratios, lymphocyte ratios and LMR.
*: *P* trend when assigning the median value to each quartile and entered as a continuous variable in the models.

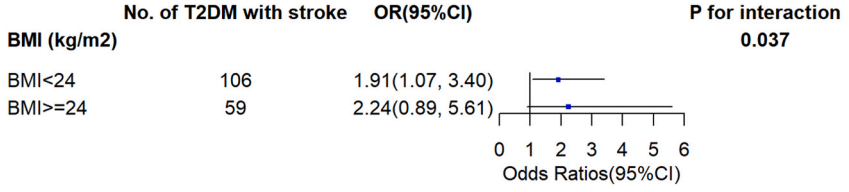


Fig. 1. Adjusted odds ratio for stroke risk according to SF in the subgroup of different levels of BMI.

glucose metabolism was reported in previous studies [10,23]. However, the evidence of the relationship between SF and ischemic stroke among individuals with T2DM were very limited. In current study, we not only found that SF level in T2DM patients with stroke was significantly higher than that in diabetes patients without stroke, but also found a significant positive association between SF level and ischemic stroke in T2DM patients after adjusting for potential confounders which suggested that SF may be an independent risk factor for ischemic stroke in T2DM patients. The mechanism underlying the positive association between SF and stroke risk among T2DM patients is still largely undefined, one explanation for this phenomenon is that iron overload can cause damage by formatting of reactive oxygen species which further promote the development of stroke [6,8]. However, considering that this study is a cross-sectional study, and recent study suggests that SF arises from damaged cell [24], the exact relationship and mechanisms of the SF

and the occurrence and development of stroke among T2DM patients remained to be explored in further cohort study. Numerous studies showed that neutrophils, lymphocytes, monocytes, neutrophil to lymphocyte ratio, and lymphocyte to monocyte ratio are potential novel biomarkers of baseline inflammatory process and could serve as outstanding predictors in patients with ischemic stroke [25–27]. In this study, we found that SF level was significantly negatively correlated with lymphocyte count, lymphocyte ratio and lymphocyte monocyte ratio, while it was significantly positively correlated with neutrophil ratio. This suggests, to some extent, the potential relationship between SF and the body's inflammatory response and state, and there are indeed studies that have found and emphasized that the level of serum ferritin will increase significantly in the reaction of inflammation and/or various diseases [24]. However, we noted no attenuation of our estimates when we adjusted for above biomarkers of inflammatory process, which remind us that it is necessary and urgent to further explore the exact mechanism of increased stroke risk caused by elevated SF levels among T2DM patients.

Additionally, subgroup analyses indicated that the positive association between SF levels and stroke risk was more pronounced among subjects with lower levels of BMI. We could not explain the definite reasons for the potential antagonistic effect between higher levels of BMI and plasma iron shown by the interaction analysis. One possible explanation is the positive association between BMI and the risk of stroke masked the role of SF in increasing the risk of stroke. Additionally, many studies and reviews have indicated that the serum iron level of adults with higher BMI (especially adult women) is lower [28,29] which may explain the antagonistic interaction between BMI and SF levels in our study. More studies are needed to further illustrate this finding.

There were some limitations to our study. Firstly, this is a cross-sectional study and the sample size is small, thus the reverse causation is an inherent limitation. Secondly, the duration of T2DM, family history of T2DM, medical treatment, and other confounding variables cannot be included completely. So, we were unable to adjust for all relevant confounding variables. Thirdly, this study was conducted in one institution and, consequently, the findings cannot be generalized to all Chinese regions. Therefore, it is meaningful for us to establish a muti-center cohort in the coming research.

5. Conclusion

In conclusion, we reported here that SF was independently associated with ischemic stroke risk among individuals with T2DM. Further prospective investigations with larger sample size are required to verify the results observed in current study. And in vivo and in vitro studies are needed to explore the underlying mechanisms exact mechanism of increased stroke risk caused by elevated SF levels among T2DM patients.

Statement of ethics

All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval No. 2022200). The data are anonymous, and the requirement for informed consent was therefore waived.

Funding

This work was supported by the National Natural Science Foundation of China (grant numbers: 82103934) and the Natural Science Basic Research Program in Shaanxi Province of China (grant numbers: 2024JC-YBQN-0961).

Data availability statement

All data generated or analyzed during this study are included in this article which is not deposited into a publicly available repository. Further enquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Youyou Zhang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Hui Wang:** Writing – review & editing. **Ruirui Jia:** Data curation. **Dong Chen:** Data curation. **Zhaoyang Li:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A.A. Motala, K. Ogurtsova, et al., Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition, Diabetes Res. Clin. Pract. 157 (2019) 107843.

[2] T.T. van Sloten, S. Sedaghat, M.R. Carnethon, L.J. Launer, C.D.A. Stehouwer, Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression, Lancet Diabetes Endocrinol. 8 (4) (2020) 325–336.

[3] A.K. Boehme, C. Esenwa, M.S. Elkind, Stroke risk factors, genetics, and prevention, Circ. Res. 120 (3) (2017) 472–495.

[4] X. Lin, H. Wang, X. Rong, R. Huang, Y. Peng, Exploring stroke risk and prevention in China: insights from an outlier, Aging 13 (11) (2021) 15659–15673.

[5] S. Wu, B. Wu, M. Liu, Z. Chen, W. Wang, C.S. Anderson, P. Sandercock, Y. Wang, Y. Huang, L. Cui, et al., Stroke in China: advances and challenges in epidemiology, prevention, and management, Lancet Neurol. 18 (4) (2019) 394–405.

[6] A. Carocci, A. Catalano, M.S. Sinicropi, G. Genchi, Oxidative stress and neurodegeneration: the involvement of iron, Biometals 31 (5) (2018) 715–735.

[7] E.C. Theil, The ferritin family of iron storage proteins, Adv. Enzymol. Relat. Area Mol. Biol. 63 (1990) 421–449.

[8] I. García-Yébenes, M. Sobrado, A. Moraga, J.G. Zarruk, V.G. Romera, J.M. Pradillo, N. Perez de la Ossa, M.A. Moro, A. Dávalos, I. Lizasoain, Iron overload, measured as serum ferritin, increases brain damage induced by focal ischemia and early reperfusion, Neurochem. Int. 61 (8) (2012) 1364–1369.

[9] M.N. Garcia-Casal, S.R. Pasricha, R.X. Martinez, L. Lopez-Perez, J.P. Peña-Rosas, Serum or plasma ferritin concentration as an index of iron deficiency and overload, Cochrane Database Syst. Rev. 5 (5) (2021) Cd011817.

[10] F.J. Yu, M.C. Huang, W.T. Chang, H.F. Chung, C.Y. Wu, S.J. Shin, C.C. Hsu, Increased ferritin concentrations correlate with insulin resistance in female type 2 diabetic patients, Ann. Nutr. Metab. 61 (1) (2012) 32–40.

[11] N. Sanjeevi, J. Freeland-Graves, S.N. Beretvas, P.K. Sachdev, Trace element status in type 2 diabetes: a meta-analysis, J. Clin. Diagn. Res. : J. Clin. Diagn. Res. 12 (5) (2018) Oe01–oe08.

[12] M. Qian, M. Liu, J.W. Eaton, Transition metals bind to glycated proteins forming redox active "glycochelates": implications for the pathogenesis of certain diabetic complications, Biochem. Biophys. Res. Commun. 250 (2) (1998) 385–389.

[13] Q. Liu, L. Sun, Y. Tan, G. Wang, X. Lin, L. Cai, Role of iron deficiency and overload in the pathogenesis of diabetes and diabetic complications, Curr. Med. Chem. 16 (1) (2009) 113–129.

[14] Y. Zheng, X.K. Li, Y. Wang, L. Cai, The role of zinc, copper and iron in the pathogenesis of diabetes and diabetic complications: therapeutic effects by chelators, Hemoglobin 32 (1–2) (2008) 135–145.

[15] T. Carbonell, R. Rama, Iron, oxidative stress and early neurological deterioration in ischemic stroke, Curr. Med. Chem. 14 (8) (2007) 857–874.

[16] E. Millerot, A.S. Prigent-Tessier, N.M. Bertrand, P.J. Faure, C.M. Mossiat, M.E. Giroud, A.G. Beley, C. Marie, Serum ferritin in stroke: a marker of increased body iron stores or stroke severity? J. Cerebr. Blood Flow Metabol. 25 (10) (2005) 1386–1393.

[17] M. Castellanos, N. Puig, T. Carbonell, J. Castillo, J. Martinez, R. Rama, A. Dávalos, Iron intake increases infarct volume after permanent middle cerebral artery occlusion in rats, Brain Res. 952 (1) (2002) 1–6.

[18] M.H. Selim, R.R. Ratan, The role of iron neurotoxicity in ischemic stroke, Ageing Res. Rev. 3 (3) (2004) 345–353.

[19] C.M. Morris, J.M. Candy, A.B. Keith, A.E. Oakley, G.A. Taylor, R.G. Pullen, C.A. Bloxham, A. Gocht, J.A. Edwardson, Brain iron homeostasis, J. Inorg. Biochem. 47 (3–4) (1992) 257–265.

[20] D.L. van der A, D.E. Grobbee, M. Roest, J.J. Marx, H.A. Voorbij, Y.T. van der Schouw, Serum ferritin is a risk factor for stroke in postmenopausal women, Stroke 36 (8) (2005) 1637–1641.

[21] H. Shi, M. Almutairi, J. Moskovitz, Y.G. Xu, Recent advances in iron homeostasis and regulation - a focus on epigenetic regulation and stroke, Free Radic. Res. 55 (4) (2021) 375–383.

[22] H. Ding, C.Z. Yan, H. Shi, Y.S. Zhao, S.Y. Chang, P. Yu, W.S. Wu, C.Y. Zhao, Y.Z. Chang, X.L. Duan, Hepcidin is involved in iron regulation in the ischemic brain, PLoS One 6 (9) (2011) e25324.

[23] C.H. Kim, H.K. Kim, S.J. Bae, J.Y. Park, K.U. Lee, Association of elevated serum ferritin concentration with insulin resistance and impaired glucose metabolism in Korean men and women, Metab. Clin. Exp. 60 (3) (2011) 414–420.

[24] D.B. Kell, E. Pretorius, Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells, Metallomics 6 (4) (2014) 748–773.

[25] P. Gong, Y. Liu, Y. Gong, G. Chen, X. Zhang, S. Wang, F. Zhou, R. Duan, W. Chen, T. Huang, et al., The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke, J. Neuroinflammation 18 (1) (2021) 51.

[26] D. Sharma, K.J. Spring, S.M.M. Bhaskar, Neutrophil-lymphocyte ratio in acute ischemic stroke: immunopathology, management, and prognosis, Acta Neurol. Scand. 144 (5) (2021) 486–499.

[27] B. Wolff, H. Völzke, J. Lüdemann, D. Robinson, D. Vogelgesang, A. Staudt, C. Kessler, J.B. Dahm, U. John, S.B. Felix, Association between high serum ferritin levels and carotid atherosclerosis in the study of health in Pomerania (SHIP), Stroke 35 (2) (2004) 453–457.

[28] E. Aigner, A. Feldman, C. Datz, Obesity as an emerging risk factor for iron deficiency, Nutrients 6 (9) (2014) 3587–3600.

[29] H.L. Cheng, C. Bryant, R. Cook, H. O'Connor, K. Rooney, K. Steinbeck, The relationship between obesity and hypoferraemia in adults: a systematic review, Obes. Rev. 13 (2) (2012) 150–161.