Influence of Serum Ferritin and B12 Levels in the Functional Outcomes of Patients with Ruptured and Unruptured Intracranial Aneurysms

Influência dos níveis séricos de ferritina e B12 nos desfechos funcionais de pacientes com aneurismas intracranianos rotos e não rotos

Nícollas Nunes Rabelo[1] Antônio Carlos Samaia da Silva Coelho[2] Leonardo Zumerkorn Pipek[2] Joao Paulo Mota Telles[2] Natalia Camargo Barbato[3] Marcia Harumy Yoshikawa[2] Guilherme Bitencourt Barbosa[2] Manoel Jacobsen Teixeira[1] Eberval Gadelha Figueiredo[1]

[1] Division of Neurosurgery, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, São Paulo, Brazil
[2] Neurology Department, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, São Paulo, Brazil
[3] Neurology Department, Centro Universitário Faculdade das Américas, São Paulo, São Paulo, Brazil

Address for correspondence Nicollas Nunes Rabelo, MD, PhD, Serviço de Neurocirurgia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), rua Dr. Enéas de Carvalho Aguiar 255, 28, São Paulo, SP, 05403-010, Brazil (e-mail: nicollasrabelo@hotmail.com).

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Abstract

Introduction Pathological processes in the arterial wall that result in vessel dilation are the cause of intracranial aneurysms (IAs), and the risk factors for their formation and progression are not well established. Ferritin is associated with inflammation and angiogenesis; it has protective antioxidative activity, and controls cell differentiation. Vitamin B12 is related to neurological and hematological disorders; it can be used as differential diagnosis tool, and acts in the control of homocysteinemia, a predictor of worse prognosis. The present article aims to assess the correlation between serum ferritin and B12 levels and the patient's functional outcome.

Materials and Methods In the present cohort study, we assessed the serum levels of ferritin and B12, as well as the scores on the modified Rankin and Glasgow Outcome Scales at 6 months, of 2 groups, one with 19 and the other with 49 individuals, out of 401 patients treated for IA at Universidade de São Paulo from 2018 to 2019. We performed a statistical analysis, using logistic regression, to determine the aforementioned correlation.

Results In the univariable analysis, the serum levels of ferritin showed no significant impact on the functional outcome (odds ratio [OR]: 0.96 for every 100 pg/mL increase; 95% confidence interval [95%CI]: 0.761–1.210; $p = 0.732$); neither did the serum levels

Keywords
- brain aneurysm
- ruptured intracranial aneurysm
- unruptured intracranial aneurysm
- subarachnoid hemorrhage
- serum ferritin
- serum B12

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of B12 (OR: 0.998 for every 100 pg/mL increase; 95%CI: 0.826–1.206; $p = 0.987$). Moreover, no significant impact on the functional outcome was observed in the multivariable analysis regarding the serum levels of B12, age, hypertension, and aneurysm rupture (OR: 1.086 for every 100 pg/mL increase; 95%CI: 0.847–1.392; $p = 0.513$).

Conclusion We were not able to confirm a statistical correlation regarding the serum levels of ferritin and B12, and functional outcome of IA patients. These variables might be linked to other determinants of the pathophysiology of IAs, like inflammation and homocysteinemia.

Resumo

Introdução Processos patológicos na parede arterial, que resultam em dilatação dos vasos, são a causa dos aneurismas intracranianos (AIs), e os fatores de risco para a sua formação e evolução não estão bem estabelecidos. A ferritina está associada a inflamação e angiogênese, tem atividade antioxidante, e controla diferenciação celular. A vitamina B12 está relacionada a distúrbios neurológicos e hematológicos, é utilizada como ferramenta de diagnóstico, e atua no controle da homocisteinemia. Este artigo visa avaliar a correlação entre os níveis séricos de ferritina e B12 e o desfecho funcional do paciente.

Materiais e Métodos Neste estudo de coorte, analisamos os níveis séricos de ferritina e B12, assim como as pontuações nas escalas de desfechos de Rankin modificada e Glasgow aos 6 meses de 2 grupos, um com 19 e o outro com 49 indivíduos, dos 401 pacientes com AI tratados na Universidade de São Paulo de 2018 a 2019. Para determinar a já mencionada correlação, realizamos análise estatística usando regressão logística.

Resultados Na análise univariada, a ferritina sérica não resultou em impacto significativo sobre o desfecho funcional (razão de possibilidades [RP]: 0,96 para cada aumento de 100 pg/mL; intervalo de confiança de 95% [IC95%]: 0,761–1,210; $p = 0,732$), nem a B12 sérica (RP: 0,998 para cada aumento de 100 pg/mL; IC95%: 0,826–1,206; $p = 0,987$). Tampouco observou-se impacto significativo sobre o desfecho na análise multivariada usando B12 sérica, idade, hipertensão e ruptura de aneurisma (RP: 1,086 para cada aumento de 100 pg/mL; IC95%: 0,847–1,392; $p = 0,513$).

Conclusão Não foi confirmada a correlação estatística entre os níveis séricos de ferritina e de B12 e o desfecho funcional de pacientes com AI. Essas variáveis podem estar ligadas a outros determinantes da fisiopatologia do AI, como inflamação e homocisteinemia.

Palavras-chave
- aneurisma cerebral
- aneurisma intracraniano rompidoaneurisma intracraniano não rompidohemorragia subaracnóidea
- ferritina sérica
- B12 sérica

Introduction

Cerebral arteries can undergo pathological processes that involve dilation, which results in the formation of intracranial aneurysms (IAs). These conditions can progress until the arterial wall ruptures, causing intracranial bleeding, that is, aneurysmatic subarachnoid hemorrhage (aSAH).[1,2] Although most unruptured aneurysms are asymptomatic, their clinical complications, such as aSAH, result in a high mortality rate, which ranges from 40% to 50%. The existing treatment tools are microsurgery and endovascular procedures, but they also present risks, including death. The risk factors for the development of IAs are still unknown, with most affected individuals not presenting any known factors; therefore, their identification is necessary.[3–5]

Ferritin is the major iron-storage protein, and it is involved in a variety of pathophysiological processes in the human body. Elevated serum levels are related to coronary artery disease, malignancy, and poor transplantation outcomes.[6] Ferritin has an iron core in its structure; it presents ferroxidase activity and has an antioxidant function. It regulates cellular iron homeostasis, through biosynthesis and secretion, as part of a dynamic cycle of iron recycling.[7]

Ferritin may be used to monitor various diseases, because it is involved in several processes, such as: iron delivery, angiogenesis, inflammation, immunity, signaling, and cancer. It is a

proinflammatory signaling molecule/mediator; it inhibits lymphocyte and myeloid cell function, since iron is required for cell proliferation and differentiation; it also plays an important role in signal transduction and migration mediated by chemokine receptors, and it inhibits the inflammatory response by producing interleukin 10 (IL-10), which inhibits interleukin 2 (IL-2), lowering lymphocyte proliferation. In addition, ferritin is recognized as a reactant and marker of acute and chronic inflammation, and it promotes angiogenesis by binding high molecular weight kininogen (HK)/activated HK (HKa), which are cofactors of the intrinsic coagulation cascade.[8]

The possible relationship with IA formation is based on the evidence that ferritin is associated with inflammation and angiogenesis, which are processes present in the aneurysm formation cascade; it is linked to aSAH, which is one of the major consequences of ruptured aneurysms, and it is related to Kawasaki disease, a syndrome reported to be associated with coronary artery aneurysms.[9–11]

Vitamin B12 is an essential nutrient, meaning it must be ingested, since it cannot be produced by the body. It plays an important role in DNA synthesis and neurological function. Low serum levels of B12 are associated with coronary diseases, demyelination of nervous system structures, ineffective erythropoiesis, megaloblastic anemia, hyperhomocysteinemia, and hemolysis. On the other hand, high serum levels of B12 are associated with poor outcome in critically-ill patients, high levels of C-reactive protein (CRP), which is an inflammatory biomarker, chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, primary hypereosinophilic syndrome, as well as myelodysplastic syndromes and acute leukemias. Therefore, serum B12 levels may be used in the differential diagnosis or as a diagnostic hypothesis for various pathologies. Oral supplementation may be an effective treatment option, and B12 deficiency is linked to senility, increasing with age progression.[12–14] Homocysteine is associated with endothelial injury and has thrombogenic properties; thus, it is correlated with cardiovascular diseases. However t no correlations have been found with IA formation.[15]

The objective of the present study was to evaluate the influence of the serum levels of ferritin and B12 in the functional outcomes of patients with ruptured and unruptured IA.

Materials and Methods

Study Design

The present is a prospective cohort study, in which social and demographic data were collected from patient charts in the database of the Division of Neurosurgery of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) who were admitted due to SAH between January 2018 and November 2019. We also collected the serum levels of ferritin and B12 and IA rupture status upon admission. The analysis of the outcomes was performed prospectively using the modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) at 6 months.

Population Data

Data from 401 patients were analyzed: 19 individuals were included in the serum ferritin analysis (►**Fig. 1**), and 49, in the serum B12 analysis (►**Fig. 2**). The subjects were evaluated regarding the serum levels of ferritin or B12, and

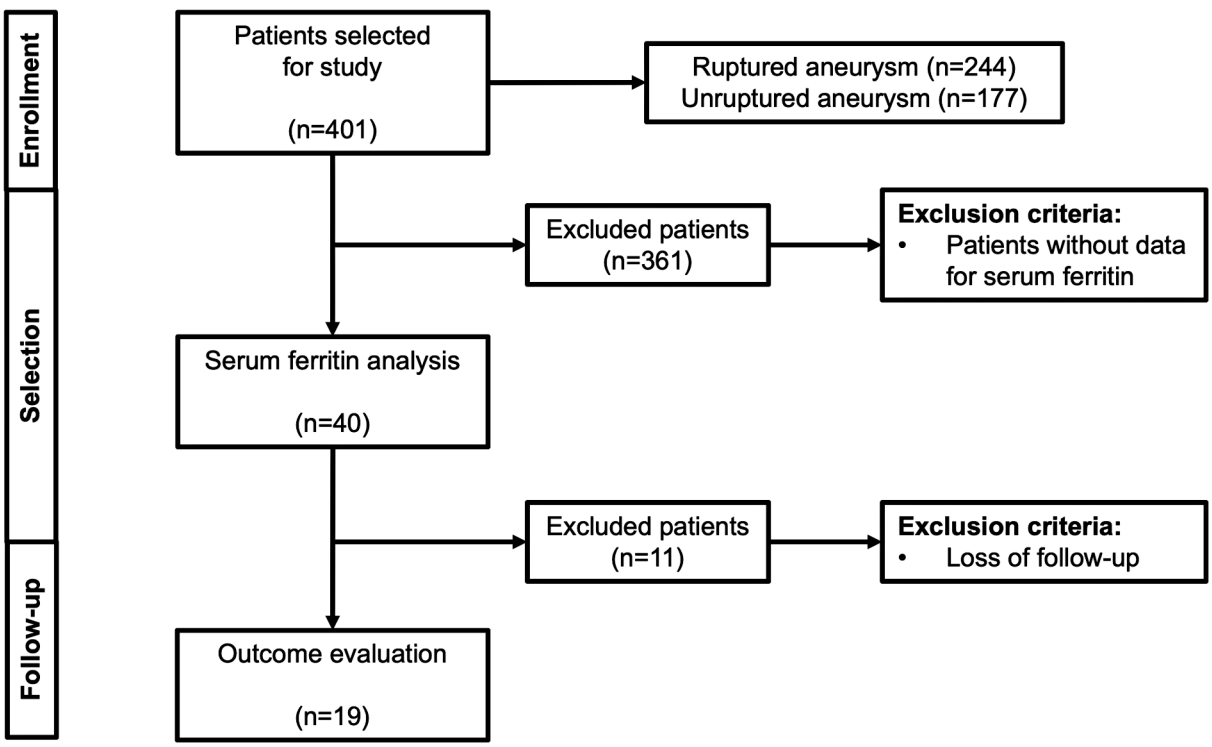

Fig. 1 Patient selection and inclusion and exclusion criteria for the ferritin analysis.

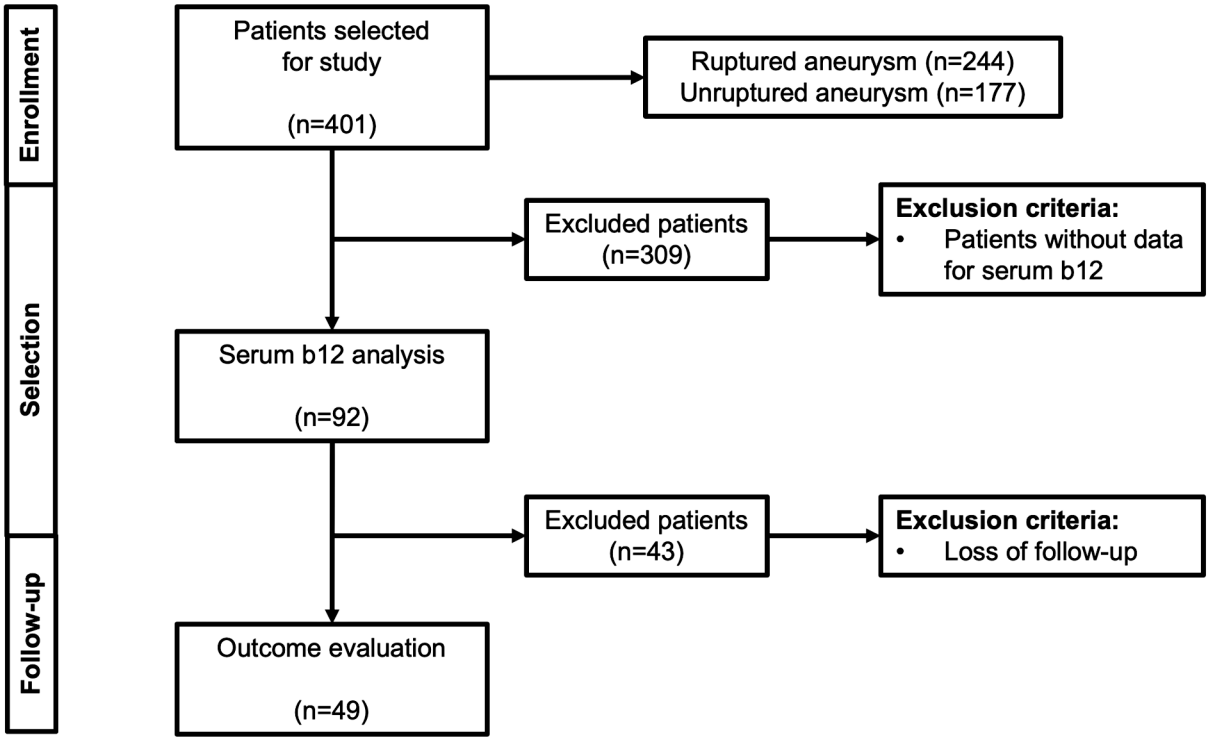

Fig. 2 Patient selection and inclusion and exclusion criteria for the B12 analysis.

the mRS and GOS scores at 6 months. Each group was subdivided into 2 groups based on their laboratory results: normal serum level or elevated serum level. For the ferritin analysis, the cut-off was a serum level of 500 ng/mL,[16] while for the B12 analysis, the cut-off was a serum level of 878 pg/mL.[17]

Exclusion Criteria

We excluded patients or whom there was no data on the serum levels of ferritin or B12 upon admission, as well as those lost to follow up in less than 6 months.

Inclusion Criteria

We included patients of both sexes and ages, with ruptured and unruptured brain aneurysms who were admitted at HCFMUSP between January 2018 and November 2019.

Statistical Analysis

We used logistic regression considering the serum levels of ferritin and B12 as independent, continuous, and binary variables. The outcomes were assessed through the scores on the mRS and GOS at 6 months. Univariate analyses for the serum levels of B12 and ferritin were performed. Moreover, a multivariate analysis including age and the presence of hypertension in the model was performed for the B12 cohort. The level of significance was established as 0.05.

Results

Serum Ferritin

The 19 patients in the ferritin group were divided into 2 subgroups based on their serum levels (normal or elevated). After stablishing a cut-off point of 500 ng/mL,[16] 17 patients were allocated in the normal ferritin level subgroup and 2 patients, in the elevated ferritin level subgroup.

Regarding the whole population analyzed, most patients were female, non-hypertensive, non-diabetic, non-smokers, with no history of hydrocephalus nor aSAH. Upon hospital admission, the median score on the Glasgow Coma Scale (GCS) was of 15, the Hunt and Hess grade was 2, and the score on the World Federation of Neurosurgical Societies (WFNS) scale was of 1. On average, at 6 months, the GOS score was of 3.6 ± 1.9, and the mRS score, of 2.9 ± 2.5. More detailed information can be found in ►**Table 1**.

Regarding the two ferritin subgroups, the major difference was that the mean WFNS score on admission was lower in the elevated subgroup (4.5) compared with the normal subgroup (2.1) ($p = 0.035$).

As shown in ►**Table 1**, the epidemiological characteristics of both groups were very similar regarding all parameters ($p > 0.05$), except for serum ferritin. We performed separate analyses for each outcome considering the impact of serum ferritin on the mRS and GOS scores at 6 months. The influence of serum ferritin on the mRS score at six months was analyzed through univariate logistic regression for the prediction of unfavorable outcomes six months after the IA. Higher serum levels of ferritin did not have an impact on the outcome (odds ratio [OR]: 0.96 for every 100 pg/mL increase; 95% confidence interval [95%CI]: 0.7611.210; $p = 0.732$) (►**Table 2**).

Serum B12

The 49 patients in the B12 group were divided into 2 subgroups based on their serum B12 levels (normal or elevated). After establishing a cut-off point of 878 pg/mL,[17,18] 43 patients were

Table 1 Characteristics and variables associated with the outcomes of patients with normal and elevated serum levels of ferritin

Variable	Normal	Elevated	*p*-value
Number of patients	17	2	
Age in years	59.1 ± 10.4	63.0 ± 1.4	0.1857
Female sex	87.5%	50%	0.3137
Aneurysm rupture	41.2%	100%	0.2105
Hypertension	41.7%	50%	1.0
Diabetes mellitus	16.7%	50%	0.3956
Smoker	25%	50%	0.5055
Hydrocephalus	7.7%	100%	0.1429
Previous subarachnoid hemorrhage	0	0	–
Score on the Glasgow Coma Scale on admission	12.5 ± 3.8	9.5 ± 3.5	0.4123
Hunt and Hess grade on admission	2.4 ± 1.3	2.0 ± 1.4	0.7486
Score on the World Federation of Neurosurgical Societies scale on admission	2.1 ± 1.6	4.5 ± 0.7	0.7486
Score on the Glasgow Outcome Scale at 6 months	3.4 ± 1.8	4.0 ± 1.4	0.6921
Score on the modified Rankin Scale at 6 months	3.0 ± 2.2	3.0 ± 2.8	1.0

Note: Data are presented as numbers or percentages, except for age and the scores on the scales and the Hunt and Hess grade, which are presented as mean ± standard deviation values.

Table 3 Characteristics and variables associated with the outcomes of patients with normal and elevated serum levels of vitamin B12

Variable	Normal	Elevated	*p*-value
Number of patients	43	6	
Age in years	59.0 ± 11.2	57.0 ± 12.4	0.718
Female sex	80.5%	83.3%	0.718
Hypertension	58.8%	66.6%	1.0
Diabetes mellitus	17.6%	16.7%	1.0
Smoker	19.4%	33.3%	1.0
Hydrocephalus	24.2%	20.0%	1.0
Previous subarachnoid hemorrhage	5.9%	0%	1.0
Score on the Glasgow Coma Scale on admission	13.3 ± 2.6	14.3 ± 1.0	0.222
Hunt and Hess grade on admission	2.2 ± 1.1	2.0 ± 1.2	0.816
Score on the World Federation of Neurosurgical Societies scale on admission	1.9 ± 1.3	1.8 ± 1.0	0.766
Score on the Glasgow Outcome Scale at 6 months	3.0 ± 1.6	4.5 ± 0.9	0.187
Score on the modified Rankin Scale at 6 months	2.5 ± 2.1	1.8 ± 1.3	0.325

Note: Data are presented as numbers or percentages, except for age and the scores on the scales and the Hunt and Hess grade, which are presented as mean ± standard deviation values.

Table 2 Univariate logistic regression for the prediction of unfavorable outcomes at 6 months after intracranial aneurysm with serum ferritin as an independent variable

Coefficients	Estimate	*p*-value
Intercept	−0.009	–
Serum ferritin (for every 100 pg/mL)	−0.040	0.732

allocated in the normal B12 level subgroup, and 6 patients, in the elevated B12 level subgroup.

Regarding the whole population analyzed, most patients were female, hypertensive, non-diabetic, non-smokers, with no history of hydrocephalus nor SAH. Upon hospital admission, the median GCS score was of 14, the Hunt and Hess grade was 2, and the WFNS score was of 2. At 6 months, the average GOS score was of was of 4.0 and the average mRS score was of 2.4.

The normal and elevated serum B12 level subgroups were similar to each other. More detailed information can be found in ►**Table 3**.

As shown in ►**Table 3**, the groups were very similar regarding all parameters, with no statistically significant values ($p > 0.05$) other than the serum level of B12. The (univariate) analysis was performed considering the impact of the serum level o B12 on the mRS score at 6 months.

We analyzed the influence of serum B12 on the mRs score at six months for the entire B12 group (►**Table 4**–model 1). The OR for every 100 pg/mL increase was of 0.998 (95%CI: 0.826–1.206; $p = 0.987$).

The multivariate analysis regarding the mRs score at 6 months, serum B12 levels, age (considering a 60-year cut), hypertension, and aneurysm rupture in the model (►**Table 4**–model 2) was also evaluated. There were no statistically significant findings ($p > 0.05$). Hypertension was the closest to significancy (OR = 7.23; 95%CI: 0.741–70.684; $p = 0.088$). The OR for every 100 pg/mL increase in the serum level of B12 was of 1.086 (95%CI: 0.847–1.392; $p = 0.513$).

Discussion

The serum levels of ferritin and B12 did not appear to change the mRS or GOS scores at six months among the IA patients included in the present analysis. Although the serum levels of ferritin were not observed to be a proper indicator of the

Table 4 Model 1: Logistic regression with serum B12 as an independent variable. Model 2: Multivariate logistic regression with serum B12, age, hypertension, and aneurysm rupture as independent variables

Model 1		
Coefficients	**Estimate**	***p*-value**
Intercept	−0.534	–
Serum B12 (for every 100 pg/mL)	−0.001	0.987
Model 2		
Coefficient	**Estimate**	***p*-value**
Intercept	−4.364	–
Serum B12 (for every 100 pg/mL)	0.082	0.513
Age (> 60 years)	1.263	0.189
Aneurysm rupture	0.938	0.335

patient's functional outcome, they might still be correlated in some way with the formation and progression of IAs. In its conjugated form, heavy-chain ferritin (HFn) may contribute to a better magnetic resonance imaging (MRI) examination, since it is associated to inflammation and angiogenesis, being a positive indicator of atherosclerosis and aneurysm diseases.[9] Ferritin oxidates and stores redox-active iron, reducing oxidative stress, which is linked to heme and endoplasmic reticulum stress. These processes are correlated to vasculopathies such as atherosclerosis, diabetes, and vascular brain events, such as IAs.[19] Higher serum levels of ferritin in the cerebrospinal fluid have been reported after the occurrence of SAH, which is one of the most dangerous consequences of IA rupture.[10] In adults, high serum levels of ferritin are related to Kawasaki disease, a syndrome associated with coronary artery aneurysms.[11] Finally, total iron binding capacity (TIBC) has been reported to be significantly and inversely associated with IA rupture, but no significant association regarding the serum levels of iron and ferritin were observed.[20]

Just like the serum levels of ferritin levels, those of vitamin B12 do not seem to determine the prognosis of IA patients, but could be associated with IA pathogenesis. Vitamin B12 analog neutralizes radicals, preventing aortic wall degeneration by scavenging free radicals and having antioxidant properties.[21] Pyridoxal 5-phosphate (vitamin B6) is an independent risk factor for abdominal aortic aneurysm (AAA).

Aneurysm are formed after the elastic lamellae of the vascular wall are degraded and the collagen production is enhanced. Vitamin B6 is responsible for lysyl oxidase, the enzyme that leads to cross-linking collagen and elastin, enabling the formation of aneurysms. Lower levels of B6 inhibit lysyl oxidase and prevent the formation of AAAs.[22]

Homocysteine

Homocysteine is an amino acid, and its irregular metabolism can lead to high pathological levels. Hyperhomocysteinemia is associated with atherosclerosis, hypertension, vascular calcification, and aneurysm formation. The pathogenic mechanism of hyperhomocysteinemia involves oxidative stress, generating vascular inflammation, stress of the endoplasmic reticulum, methylation, and demethylation of genes, altering their expressiveness, and altering protein functions.[23] High homocysteine levels have been reported in 68% of AAA patients.[24] However, there is no consensus in the literature regarding the relationship between vitamin B12 and homocysteine levels. Even though some articles argue that there is no relationship between B12 and homocysteine and, accordingly, neither there is one between B12 and aneurysms,[25–27] others support the hypothesis that higher levels of B12 generate lower levels of homocysteine; therefore, they indicate vitamin supplementation as a protective tool.[24,28,29] Moreover, a significant inverse correlation between B12 levels and the maximum diameter of unruptured AAAs has been reported.[30]

Limitations of the Study

A limitation of the present study is that data was only collected from one reference center in the city of São Paulo, Brazil. Another limitation is that the study involved prospective collection of data from charts, which makes certain biases inevitable. Also, some charts were lacking information. Furthermore, only a minority of patients met all inclusion criteria, and some were lost follow-up before the analysis at six months, which resulted in a small sample, restricting the strength of the conclusions of the present article. However, to the best of our knowledge, the present is the first study to analyze the influence of the serum levels of ferritin and B12 in the functional outcome of patients with ruptured and unruptured IAs.[31]

Conclusion

The serum levels of ferritin and B12 levels do not seem to have an impact on the long-term outcomes after SAH. Despite that, ferritin and B12 may still be associated with the pathophysiological process of aneurysm formation, since they are correlated to the inflammatory process and homocysteine levels. Therefore, broader future investigations regarding these relationships may still be promising.

Ethical Standards

The present research project was approved by the Ethics and Research Committee of HCFMUSP (online registration CAPPesq: 15226–approved on 06/20/2016); it is registered on Plataforma Brasil under CAAE number: 61719416.6.0000.0068.

Disclosure

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Originality

The present manuscript is a unique submission and is not being considered for publication in any other source in any medium.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. Neurology 2016;87(11):1118–1123. Doi: 10.1212/WNL.0000000000003091

2 Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. Stroke 2014;45(07):1958–1963. Doi: 10.1161/STROKEAHA.114.005318

3 Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8(07):635–642. Doi: 10.1016/S1474-4422(09)70126-7

4 Naggara ON, Lecler A, Oppenheim C, Meder JF, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: a systematic review of the literature on safety with emphasis on subgroup analyses. Radiology 2012;263(03):828–835. Doi: 10.1148/radiol.12112114

5 Kotowski M, Naggara O, Darsaut TE, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. J Neurol Neurosurg Psychiatry 2013;84(01):42–48. Doi: 10.1136/jnnp-2011-302068

6 Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood Rev 2009;23(03):95–104. Doi: 10.1016/j.blre.2008.08.001

7 Arosio P, Elia L, Poli M. Ferritin, cellular iron storage and regulation. IUBMB Life 2017;69(06):414–422. Doi: 10.1002/iub.1621

8 Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta 2010;1800(08):760–769. Doi: 10.1016/j.bbagen.2010.03.011

9 Kitagawa T, Kosuge H, Uchida M, et al. RGD targeting of human ferritin iron oxide nanoparticles enhances in vivo MRI of vascular inflammation and angiogenesis in experimental carotid disease and abdominal aortic aneurysm. J Magn Reson Imaging 2017;45(04):1144–1153. Doi: 10.1002/jmri.25459

10 Petzold A, Worthington V, Appleby I, Kerr ME, Kitchen N, Smith M. Cerebrospinal fluid ferritin level, a sensitive diagnostic test in late-presenting subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2011;20(06):489–493. Doi: 10.1016/j.jstrokecerebrovasdis.2010.02.021

11 Cunha BA, Pherez FM, Alexiadis V, Gagos M, Strollo S. Adult Kawasaki's disease with myocarditis, splenomegaly, and highly elevated serum ferritin levels. Heart Lung 2010;39(02):164–172. Doi: 10.1016/j.hrtlng.2009.06.007

12 Zulfiqar AA, Andres E, Lorenzo Villalba N. Hipervitaminosis B12. Nuestra experiencia y una revisión [Hypervitaminosis B12. Our experience and a review]. Medicina (B Aires) 2019;79(05):391–396

13 Romain M, Sviri S, Linton DM, Stav I, van Heerden PV. The role of Vitamin B12 in the critically ill–a review. Anaesth Intensive Care 2016;44(04):447–452. Doi: 10.1177/0310057. Doi: X1604400410

14 Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician 2003;67(05):979–986

15 Rosi J, Morais BA, Pecorino LS, et al. Hyperhomocysteinemia as a Risk Factor for Intracranial Aneurysms: A Case-Control Study. World Neurosurg 2018;119:e272–e275. Doi: 10.1016/j.wneu.2018.07.132

16 Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Peña-Rosas JP. Are Current Serum and Plasma Ferritin Cut-offs for Iron Deficiency and Overload Accurate and Reflecting Iron Status? A Systematic Review. Arch Med Res 2018;49(06):405–417. Doi: 10.1016/j.arcmed.2018.12.005

17 Mwafy SN, Afana WM. Hematological parameters, serum iron and vitamin B_{12} levels in hospitalized Palestinian adult patients infected with *Helicobacter pylori*: a case-control study. Hematol Transfus Cell Ther 2018;40(02):160–165. Doi: 10.1016/j.htct.2017.11.010

18 Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington (DC): National Academies Press (US); 1998. PMID: 23193625

19 Gáll T, Balla G, Balla J. Heme, Heme Oxygenase, and Endoplasmic Reticulum Stress-A New Insight into the Pathophysiology of Vascular Diseases. Int J Mol Sci 2019;20(15):3675. Doi: 10.3390/ijms20153675

20 Can A, Lai PMR, Castro VM, et al. Decreased Total Iron Binding Capacity May Correlate with Ruptured Intracranial Aneurysms. Sci Rep 2019;9(01):6054. Doi: 10.1038/s41598-019-42622-y

21 Schwaerzer GK, Kalyanaraman H, Casteel DE, et al. Aortic pathology from protein kinase G activation is prevented by an antioxidant vitamin B_{12} analog. Nat Commun 2019;10(01):3533. Doi: 10.1038/s41467-01911389-1

22 Peeters AC, van Landeghem BA, Graafsma SJ, et al. Low vitamin B6, and not plasma homocysteine concentration, as risk factor for abdominal aortic aneurysm: a retrospective case-control study. J Vasc Surg 2007;45(04):701–705. Doi: 10.1016/j.jvs.2006.12.019

23 Fu Y, Wang X, Kong W. Hyperhomocysteinaemia and vascular injury: advances in mechanisms and drug targets. Br J Pharmacol 2018;175(08):1173–1189. Doi: 10.1111/bph.13988

24 Warsi AA, Davies B, Morris-Stiff G, Hullin D, Lewis MH. Abdominal aortic aneurysm and its correlation to plasma homocysteine, and vitamins. Eur J Vasc Endovasc Surg 2004;27(01):75–79. Doi: 10.1016/j.ejvs.2003.09.001

25 Roohi J, Kang B, Bernard D, Bedja D, Dietz HC, Brody LC. Moderately Elevated Homocysteine Does Not Contribute to Thoracic Aortic Aneurysm in Mice. J Nutr 2017;147(07):1290–1295. Doi: 10.3945/jn.117.251173

26 Spark JI, Laws P, Fitridge R. The incidence of hyperhomocysteinaemia in vascular patients. Eur J Vasc Endovasc Surg 2003;26(05):558–561. Doi: 10.1016/s1078-5884(03)00381-2

27 Takagi H, Umemoto TAlice (All-Literature Investigation of Cardiovascular Evidence) group. Vitamins and abdominal aortic aneurysm. Int Angiol 2017;36(01):21–30. Doi: 10.23736/S0392-9590.16.03618-X

28 Czekajło A. Role of diet-related factors in cerebral aneurysm formation and rupture. Rocz Panstw Zakl Hig 2019;70(02):119–126. Doi: 10.32394/rpzh.2019.0061

29 Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. Nutr Metab (Lond) 2017;14:78. Doi: 10.1186/s12986-017-0233-z

30 Lindqvist M, Hellström A, Henriksson AE. Abdominal aortic aneurysm and the association with serum levels of Homocysteine, vitamins B6, B12 and Folate. Am J Cardiovasc Dis 2012;2(04):318–322

31 Ajiboye N, Chalouhi N, Starke RM, Zanaty M, Bell R. Unruptured Cerebral Aneurysms: Evaluation and Management. ScientificWorldJournal 2015;2015:954954. Doi: 10.1155/2015/954954

