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Original article

Heart failure, micronutrient profile, and its connection with thyroid dysfunction and nutritional status☆

Livia Fernandes de Lima [a,*], Fernando Barbosa Júnior [b], Marcus Vinícius Simões [a], Anderson Marliere Navarro [a]

[a] Department of Internal Medicine, Medical School of Ribeirão Preto, Avenida Bandeirantes 3900, Monte Alegre, 14049-900 Ribeirão Preto, SP, Brazil
[b] Department of Clinical, Toxicological and Bromatological Analyses, Faculty of Pharmacy of Ribeirão Preto, Avenida do Café s/n, Monte Alegre, 14049-903 Ribeirão Preto, SP, Brazil

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SUMMARY

Introduction: Heart failure (HF) is a growing public health issue; its risk factors include inappropriate dietary intake of microelements such as iodine, selenium, zinc and iron, which may lead to thyroid dysfunction.
Objective: This study aimed to assess the correlation among the functional class stages of patients with HF, iodine, selenium, iron and zinc levels with the presence of thyroid dysfunction.
Methodology: One hundred nine patients from the HF outpatient clinic of the Clinics Hospital of Ribeirão Preto whose blood and urine were collected for micronutrient analysis and laboratory tests were selected. The subjects' weight and height were also measured to calculate their BMI. First, a descriptive analysis of the data was made into tables, and then statistical analyses were done at a 5% significance level ($p < 0.05$).
Results: Most patients whose data was analysed were elderly and overweight. Excess ioduria, serum selenium and zinc, erythrocyte zinc and deficiency in serum iron and erythrocyte selenium were observed. The prevalence of thyroid dysfunction was 8.3%. Multivariate logistic regression verified that thyroid dysfunction increases the chance of classification in functional class III or IV ($p = 0.015$; OR = 8.72) by 8.7 times; each year of age increases the chance by 4.6% of classification in functional class III or IV ($p = 0.008$; odds ratio [OR] = 1.05), and each unit of BMI increases the chance of classification in functional class III or IV by 9.2% ($p = 0.028$; OR = 1.09).
Conclusion: Patients with HF were deficient in serum iron and erythrocyte selenium. No connection was found between hypothyroidism and mineral deficiency, which seems to be related more to the severity of the disease than to the micronutrient nutritional profile.

1. Introduction

Heart failure (HF) is a clinical syndrome characterised by impaired blood-filling or ejection capacity in the ventricle and, consequently, may lead to insufficient blood supply to meet the metabolic needs of tissues [4,14]. It is a large and growing public health issue [7,26]; after the first hospital admission due to this pathology, patients' survival rate is worse than for most types of cancer [23]. Worldwide, an estimated 23 million people have HF, and 5700 new cases are confirmed every year [26].

Patients with HF may have functional, anatomic, and biological alterations associated with emotional and social factors that affect their nutritional status. Studies have shown that older patients with this pathology have lower dietary intake of proteins and calories than healthy older people [17]. Lourenço et al. [20] showed the prevalence of major inadequacy of some analysed micronutrients, including iodine, zinc and iron, among patients with HF.

In addition to dietary habits, other factors such as structural and functional alterations of the gastrointestinal tract, as in the terminal

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* Corresponding author.
E-mail address: livia.lima@usp.br (L.Fd. Lima).

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ileum, colon and sigmoid, and increased intestinal wall thickness can be observed in some patients, which suggests the presence of loop oedema and involves intestinal permeability abnormalities that impair the absorption of nutrients. In addition, the use of some medications, such as amiodarone, by patients with HF may affect mineral metabolism [29,32].

Besides inappropriate intake, altered metabolism and drug interactions, the clinical evolution of patients with HF in general presents the proinflammatory status, increased oxidative stress and greater nutrient loss that generally lead to variable degrees of malnourishment [33].

All these factors in patients with HF can decrease the absorption of micronutrients, such as iodine, selenium, zinc and iron, which would directly affect the formation of thyroid hormones [40]. Iodine is reduced to iodide at the apical surface of the thyroid cell. This process is catalysed by thyroid peroxidase, an iron-dependent enzyme in hydrogen peroxide, which is dangerous to the thyroid and therefore receives control of glutathione peroxidase, a sialoprotein. This process will generate thyroid hormones: triiodothyronine (T3) and thyroxine (T4) that expel them from the thyroid and transform T4 into T3 (the active hormone), which requires the presence of deiodinases I and II, dependent on selenium and zinc [16].

Therefore, HF can affect the production of thyroid hormones, which is why this study aimed to assess the relationship between the functional class stages of patients with HF and iodine, selenium, iron and zinc levels with the presence of thyroid dysfunction.

2. Methodology

2.1. Study population

For the sample calculation, the concentrations of thyroid stimulating hormone (TSH) were considered. Through a pilot study, serum TSH values were verified in patients with heart failure, and those who had a concentration of TSH between 0.4 and 4 μU/mL were considered euthyroid; greater than 4 μU/mL were classified with hypothyroidism. According to Singer's equation (2001), which compares mean and variance of TSH in these two groups, and considering the significance level of 0.05 and test power of 0.80, the sample size was calculated to be 110 patients.

This is a cross-sectional study conducted from August 2013 to July 2014 at the Clinics Hospital of Ribeirão Preto Medical School, University of São Paulo. A convenient sampling was done. Every patient over 18 years old of both sexes, with stable heart failure being followed by the Heart Failure Outpatient Clinic for at least three months after the most recent hospital admission, who agreed with the terms of free and informed consent (TFIC) were recruited. Patients who were taking amiodarone or levothyroxine, those who had undergone thyroidectomy, who had kidney failure, liver disease, and/or collagenosis or second medical records were excluded. Thus, 109 patients were analysed.

2.2. Study groups

The patients were split based on their functional class. According to the New York Heart Association (NYHA), patients with HF are classified into four functional classes according to how much limitation in daily activities the disease imposes, ranging from Class I to Class IV [4]. The higher the class, the fewer daily activities the person is able to perform. The patients were separated according to their functional class: functional classes I and II (FCGA) and functional classes III and IV (FCGB).

2.3. Ethical considerations

Because the research involved humans, the present study was approved by the Research Ethics Committee of the Clinics Hospital of the Medical School of Ribeirão Preto under process no. 14417313.6.0000.5440, opinion no. 359593, on August 14, 2013. The TFIC was also approved in the same process.

2.4. Anthropometric, biochemical, and clinical data

The cross-sectional study was carried out over 12 months. The routine biochemical tests were performed at the Central Laboratory of the Clinics Hospital of Ribeirão Preto. The glycaemia, urea, albumin, total proteins and creatinine phosphokinase (CPK) tests used the oxidase/peroxidase, glutamate dehydrogenase enzyme (urease/GLDH), bromocresol green, biuret and creatinine kinase by UV kinetic–increasing reaction according to the International Federation of Clinical Chemistry and Laboratory Medicine (CK-NAC UV-IFCC) methods, respectively. Creatinine levels were measured by Jaffe reaction. Flow cytometry was used for the complete blood count, whereas direct and indirect bilirubin was measured by DiaSys – DCA. C-reactive protein C (CRP) was measured using high-sensitivity turbidimetry assay.

Information about medication use, personal background, cause of heart failure and functional class of each participant was taken from the patient's file. Patient weight and height were measured by the researcher by using a digital balance by Toledo Prix® (São Bernardo do Campo, SP, Brazil) and fixed stadiometer by Welmy® (Santa Bárbara d'Oeste, SP, Brazil), respectively, to calculate the body mass index (BMI).

Biochemical analyses concerning thyroid function (TSH, free T4 and anti-thyroperoxidase antibodies [anti-TPO]) were performed at the Thyroid Laboratory/Neonatal Screening of the Clinics Hospital of Ribeirão Preto, using the chemiluminescence method (IMMULITE® 2000, DPC) in a single assay by using third-generation TSH, F4Free, and ATA kits to measure TSH, free T4, and anti-TPO. As a result, the intra-assay coefficient of variation values was 4.68% for TSH, 2.77% for T4, and 8.89% anti-TPO.

The inductively coupled plasma spectrometry method (ICP-MS ELAN 6100 Sciex® [PerkinElmer Instruments, 71 Ribeirão Preto, SP, Brazil]) was used to measure urine levels of iodine and serum and erythrocyte levels of zinc, selenium and iron at the Laboratory of Clinical, Toxicological and Bromatological Analyses of the Faculty of Pharmacy of Ribeirão Preto [5]. The intra-assay coefficient of variation values are iodine 0.128%, selenium 6.22%, zinc 2.31%, serum iron 3.3%, selenium 0.12%, erythrocyte zinc 0.86% and iron 1.5%.

After the analysis of erythrocyte minerals, the concentration of haemoglobin (Hb) per litre of blood was obtained using the following formula:

$$\text{Hb (g/L)} = \frac{\text{erythrocyte iron}}{4}\ (\text{mol/L}) \times 64,456$$

According to Stefanowicz et al. [37], iron is measured as a surrogate for haemoglobin, whose concentration can be calculated using the preceding equation, in which 64,456 is the molecular weight of haemoglobin in grams and the denominator is the number of iron atoms per haemoglobin molecule.

The results obtained were compared with reference values, 75–110 μg/dL, 90–125 μg/L, and 50–175 μg/dL for the serum concentrations of zinc, selenium and iron, respectively. The adequate erythrocyte concentrations of zinc may be expressed in relation to haemoglobin (40–44 μg/g Hb) or volume of blood (10–14 μg/dL). The erythrocyte concentration of selenium is 90–190 μg/L. Finally, the normal range for ioduria is 100–200 μg/L [9,11,18,21,24,25,34,39].

2.5. Statistical analysis

Exploratory analysis of the data was first carried out to obtain an overview of the variation of those values by organising and describing the data in tables with descriptive measures. The mean, standard deviation and confidence interval (95%) were calculated.

After the data distribution analysis, the Kolmogorov–Smirnov test was performed to verify equality between the groups. In the data analysis, the Student's *t*-test was applied to the independent variables that followed normality, whereas the Mann–Whitney test was applied to the non-parametric independent variables. The X^2 exact test was used for the categorical variables, and multivariate logistic regression analysis was used to determine whether patients with heart failure were suffering from mineral deficiencies related to thyroid function. Significant differences were obtained at a 5% significance level ($p < 0.05$). Analysis was performed with the use of SPSS (version 19; SPSS, Inc., Chicago, IL) software.

3. Results

The number of volunteers who initially accepted participation in this study was 112; however, three of them initiated the use of amiodarone prior to blood and urine collection and had to be excluded. That reduced the sample to 109 subjects, 54.1% (59 volunteers) of whom were male and 45.9% (50 volunteers) were female. Aspects related to the patients are listed in Table 1.

Of the patients analysed, 45.8% were older, 11% were below their appropriate weight, 30.55% were within the normal weight range, 34.86% were overweight, and 14.67% were obese, according to BMI values. The biochemical tests showed mean concentration above the recommended for creatinine phosphokinase (CPK) (132.41 ± 104.67 U/L), glycaemia (117.99 ± 57.6 mg/dL), and CRP (1.23 ± 3.04 mg/dL).

Table 1
Demographic and clinical aspects of the 109 patients selected at the Heart Failure Clinic of the Clinics Hospital of Ribeirão Preto.

Demographic and clinical aspects	Volunteers ($n = 109$)
Heart failure aetiology	
Chagastic	16.51%
Diabetic/hypertensive	14.67%
Ischaemic	25.68%
Idiopathic	15.59%
Alcoholic	10.09%
Comorbidities	
Arterial hypertension	51.37%
Diabetes mellitus	27.52%
Dyslipidaemia	28.44%
Smoker	19.3%
Alcoholic	2.8%
NYHA functional class	
I	6.48%
II	51.85%
III	39.81%
IV	1.86%

In relation to minerals, according to Table 2, most patients' analysis showed signs of excess ioduria, serum selenium and zinc as well as serum iron deficiency.

After general analyses, the patients were grouped into FC I and II (57.8% of the patients: FCGA) and FC III and IV (42.2% of the patients: FCGB). Table 3 shows a correlation between the higher functional classes and the risk of developing thyroid dysfunction.

The groups based on functional class had significant differences concerning age and serum concentrations of urea and total proteins, according to the biochemical and anthropometric tests (Table 4). Tests regarding liver function (direct and indirect bilirubin) and blood count (red blood cells, haematocrits, white blood cells, mean corpuscular volume and platelets) did not significantly differ between the groups.

The different functional classes showed no significant differences in ioduria or plasma and erythrocyte selenium, zinc or iron (Table 5).

The multivariate logistic regression analysis for the dichotomised dependent variable functional class (I + II vs. III + IV) initially verified whether there is collinearity between the independent (predictor) variables. The variables with variance inflation factor (VIF) greater than 3 were excluded. After that, the multivariate logistic regression analysis was performed, and it was verified that thyroid dysfunction increases the chance of classification in functional class III or IV by 8.7 times ($p = 0.015$; OR = 8.72), each year of age increases the chance of classification in functional class III or IV by 4.6% ($p = 0.008$; OR = 1.05) and each unit of BMI increases the chance of being in functional class III or IV by 9.2% ($p = 0.028$; OR = 1.09) (Table 6).

4. Discussion

Usually, the clinical evolution of patients with HF leads to malnourishment settings due to inappropriate food intake, altered metabolism, pro-inflammatory status, increased oxidative stress, and greater loss of nutrients, including through drug interactions [33]. However, the estimates of the incidence of malnourishment associated with HF vary according to the population studied and the criteria used to define such incidence.

When assessing food intake among patients with HF, Lourenço et al. [20] reported energy intake below the daily requirements for over 60% of the cases. When that occurs, the diet may seem less varied and poor in micronutrients [31]. In this type of comorbidity, not only is intake impaired, but nutrient absorption is also. The presence of abdominal oedema, the increase in permeability, chronic inflammation of the mucosa, that is, disturbed intestinal microcirculation associated with intestinal ischaemia, may alter intestinal function and prevent the proper absorption of micro- and macronutrients [10].

In the present study, the anthropometric data showed that only 11% of the patients were malnourished according to the BMI, and there was a major prevalence of overweight volunteers (48.86%).

Table 2
Frequency of 109 patients selected at the Heart Failure Clinic of the Clinics Hospital of Ribeirão Preto with signs of deficiency, normality, and excess serum iron, selenium, zinc and ioduria.

Indicative	Selenium, *n* (%) (μg/L)	Zinc, *n* (%) (μg/dL)	Iron, *n* (%) (μg/dL)	Iodine, *n* (%) (μg/L)
Deficiency	1 (0.92%)	0	65 (59.63%)	0
Mean ± SD	52.5 ± 149.27	–	21.41 ± 76.66	–
Normality	5 (4.59%)	3 (2.75%)	24 (22.02%)	32 (29.35%)
Mean ± SD	105.56 ± 111.75	84.38 ± 118.59	105.72 ± 27.99	214.48 ± 356.67
Indicative of excess	103 (94.49%)	106 (97.25%)	20 (18.35%)	77 (70.65%)
Mean ± SD	273.32 ± 6.87	256.84 ± 3.35	324.13 ± 98.12	971.10 ± 178.33

Table 3
Comparison of the categorical variables according to functional class.

Variable	FCGA ($n = 63$)	FCGB ($n = 46$)	p
Sex			
Female	47.6%	44.4%	0.11
Male	52.4%	55.6%	
Comorbidities			
Arterial hypertension	44.4%	62.2%	0.07
Diabetes mellitus	25.4%	27.8%	0.43
Dyslipidaemia	22.2%	37.8%	0.08
Smoker	17.5%	22.5%	0.54
Alcoholic	3.2%	2.2%	1
Thyroid dysfunction			
Absence	96.8%	84.4%	0.03*
Presence	3.2%	15.6%	

FCGA: group with functional classes I and II; FCGB: group with functional classes III and IV.
*$p < 0.05$.

Table 6
Multivariate logistic regression analysis for the dichotomised dependent variable functional class (I + II vs. III + IV) with independent (predictor) variables.

Variables	B	S.E.	p	Odds	95% CI for odds	
					Lower	Upper
TSH	2.166	0.892	0.015*	8.719	1.517	50.114
Se serum	−0.012	0.010	0.245	0.988	0.968	1.008
Zn serum	0.000	0.000	0.214	1.000	1.000	1.000
Se erythrocyte	0.002	0.003	0.513	1.002	0.996	1.008
Zn erythrocyte	−0.005	0.004	0.205	0.995	0.987	1.003
Iodine	0.000	0.000	0.678	1.000	1.000	1.000
Age	0.045	0.017	0.008*	1.046	1.012	1.081
Sex	−0.323	0.544	0.553	0.724	0.249	2.104
IMC	0.088	0.040	0.028*	1.092	1.010	1.180
Urea	−0.014	0.015	0.362	0.986	0.957	1.016
Creatinine	0.134	0.781	0.864	1.143	0.247	5.282

*$p < 0.05$.

Takiguchi et al. [38] also found a much lower prevalence of volunteers below the normal weight than overweight/obese ones.

This difference could occur because all patients studied had a more stable clinical setting with preserved kidney function and proper treatment. In these cases, patients may not show malnutrition because, due to clinical stability, they are able to eat better and exhibit better nutrient absorption. Thus, the absorption of minerals involved with thyroid dysfunction may not show nutritional deficiencies and, consequently, significant differences in the results. Therefore, when analysing patients with decompensated HF, the same eating profiles and results may not be found in more stabilised patients.

Moreover, not only food intake but other factors may influence nutrient metabolism. Patients with HF may have increased oxidative stress, which will also affect microelements such as iron, selenium and zinc [19]. Although the issue has not been clarified, studies have shown that patients with HF have deficiencies of these micronutrients [35].

Studies showing anaemia and iron deficiency are common among patients with HF [1]. The deficiency of this micronutrient is the most prevalent comorbidity among patients with HF and is related to more advanced stages of the diseases and high CRP levels [22].

In this study, serum iron and erythrocyte selenium were below recommended levels, but concentrations of serum zinc and selenium were above. The half-life of erythrocytes is 120 days, and the amount of minerals they contain does not vary with recent changes [30]. However, plasma selenium levels may be altered in the

Table 4
Comparison of anthropometric and biochemical data according to the functional class.

Variables	FCGA ($n = 63$)				FCGB ($n = 46$)				p
	Mean ± SD	Median	Minimum	Maximum	Mean ± SD	Median	Minimum	Maximum	
Age[a] (years)	53.97 ± 14.31	55	18	82	60.69 ± 12.89	62	32	81	0.01*
BMI[a] (kg/m^2)	26.96 ± 5.49	26.92	15.94	42.28	28.11 ± 6.09	27.66	18.29	44.36	0.31
Albumin (g/dL)	4.13 ± 0.34	4.2	2.7	4.7	4.13 ± 0.36	4.2	3	4.8	0.89
CPK (U/L)	136.1 ± 104.81	99	30	514	123.67 ± 103.68	88	12	605	0.63
Urea (mg/dL)	48.7 ± 25.53	42	18	156	56.98 ± 23.14	54	15	105	0.01*
Creatinine (mg/dL)	1.2 ± 0.44	1.13	0.53	3.19	1.36 ± 0.44	1.31	0.75	2.59	0.1
Glycaemia (mg/dL)	123.32 ± 68.04	99	53	428	111.14 ± 38.26	98.5	76	260	0.7
CRP (mg/dL)	1.3 ± 3.2	0.32	0	15.28	1.14 ± 2.8	0.39	0	18.14	0.35
Total proteins (g/dL)	7.09 ± 0.41	7.1	5.8	7.8	6.65 ± 1.1	6.9	0.8	7.8	0.04*
TSH (μU/mL)	1.94 ± 4.26	1.34	0.1	34.8	2.24 ± 2.1	1.54	0.26	10.2	0.12

FCGA: group with functional classes I and II; FCGB: group with functional classes III and IV; *$p < 0.05$.
[a] Mean values for Student's *t*-test.

Table 5
Assessment of plasma and erythrocyte concentration of iron, selenium and zinc according to the functional class.

Variables	FCGA ($n = 63$)				FCGB ($n = 46$)				p
	Mean ± SD	Median	Minimum	Maximum	Mean ± SD	Median	Minimum	Maximum	
Plasma									
Selenium (μg/L)	261.8 ± 122.8	245.15	52.5	802.44	262.08 ± 112.37	226.16	91.53	635.43	0.99
Zinc (μg/dL)	259.44 ± 95.21	243.71	79.18	552.79	234.65 ± 72.57	237.05	84.93	372.83	0.4
Iron (μg/dL)[a]	46.6 ± 181.6	16.13	ND	747.91	11 ± 154.7	7.78	ND	472.55	0.37
Erythrocyte									
Selenium (μg/L)	64.13 ± 34.18	60.7	7.88	238.74	68.51 ± 35.93	61.89	20.71	246.43	0.052
Zinc (μg/dL)[a]	1749.28 ± 871.07	1766.85	99.71	4012.07	1966.86 ± 813.36	199.72	677.99	3837.30	0.19
Iron (μg/dL)	1583.02 ± 1181.81	1215.01	ND	5738.44	1819.58 ± 1117.02	1556.73	131.21	4498.04	0.35
Ioduria (μg/L)	712.28 ± 738.66	136.5	3849.95	394.05	736.47 ± 819.51	394.05	121.85	4184.36	0.72

ND: non-detectable; *$p < 0.05$. FCGA: group with functional classes I and II; FCGB: group with functional classes III and IV.
[a] Mean values for Student's *t*-test.

presence of systemic inflammatory response [36], which in most cases is present in patients with HF.

Duncan et al. [10] observed an inverse correlation between plasma concentration of this micronutrient and the magnitude of the inflammatory response assessed by CRP concentration. The same does not occur with erythrocyte levels of selenium. In this form, it can be inferred that most patients who are analysed are selenium-deficient.

Another important micronutrient in this study is iodine. The urinary excretion of iodine, whose main source for the Brazilian population is iodised table salt, is directly proportional to the intake of this micronutrient [8]. Excess salt intake may be harmful to patients with HF; thus, public policies have promoted sodium restriction by limiting the salt intake of those patients (<2 g salt/day) [6], which lowers the intake of iodine.

Thus, it was expected that this population would be iodine-deficient. However, most patients were found to have excess ioduria, which is also observed in the healthy population [27]. According to Basuray et al. [3], who assessed sodium intake and excretion among patients with HF, only 23% of the patients followed the recommendations, which could justify the present results.

All these micronutrients directly participate in the formation of thyroid hormones (T3 and T4) [40]. Both excess and deficiency may lead to thyroid dysfunction. Patients with HF have been shown to have prevalence of thyroid dysfunction between 1.3% and 21%, depending on their TSH level, age and iodine intake [28].

The present study found prevalence of thyroid dysfunction among patients with HF at 8.3%. Another study on the same patients who did not use amiodarone reported prevalence of 14% [12]. Both values match the study by Pasqualettiet al. [28].

This prevalence could change according to the stage of heart failure and other clinical factors. When the less severe functional classes (I and II) were compared with the more severe ones (III and IV), a significant difference was found between the groups regarding TSH, age, serum concentrations of urea and total proteins.

Iacoviello et al. [15], when relating those groups, found that more advanced functional classes are at higher risk of developing thyroid dysfunction, matching the findings of the present study. Patients in the highest classes—classes III and IV—are at a 5.62-fold higher risk of developing thyroid dysfunction than those in classes I and II.

Güder et al. [13], when comparing the different functional classes of patients with HF, observed that the patients at more advanced stages were older and had lower BMI, total cholesterol, and systolic arterial blood pressure. A study of 667 patients showed that lower classes featured younger patients with higher diastolic arterial blood pressure compared to the other functional classes, which corroborates the aforementioned study. The more advanced functional classes, in turn, had higher creatinine and urea levels compared to patients in classes I and II [2]. Both studies match the present study when age and urea are analysed. Because they also found an association of higher age and urea levels and more severe disease.

Further studies are required to investigate the relationship between nutritional status and micronutrients in HF progression and development of thyroid dysfunction, because patients with this cardiac disorder are a large fraction of the population and have a high likelihood of developing thyroid dysfunction. Investigating such causes is essential for better patient prognosis. In addition, this study has limitations because it lacked a normal control group, the dietary intake of the subjects was not recorded, and this is an observational study, which cannot establish the causal relationship between variables of interest and dietary intake.

5. Conclusion

No correlation was found of hypothyroidism and mineral deficiency with thyroid hormones among patients with HF. Thyroid dysfunction among patients with HF seems to be related more to factors linked to disease severity than to nutritional status, such as micronutrient levels, despite the prevalence of iron and selenium deficiencies.

Conflicts of interest

There is no conflict of interest.

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