

Zinc Deficiency and Anemia in Women of Reproductive Age, Cuba

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Abstract: Anemia, an unresolved health problem in Cuba, has been attributed to iron (Fe) deficiency. There is little information regarding the relationship between anemia, zinc (Zn) deficiency and the effect of inflammation on Fe and Zn deficiencies. It is intended to identify hematological manifestations of anemia, iron and zinc deficiency and its relationship with inflammation in women of reproductive age (WRA) from different provinces of Cuba. An exploratory cross-sectional study was carried out from 2016 to 2018. 654 apparently healthy women aged 18 to 40 years were selected from different provinces of Cuba through multistage cluster sampling. The following were measured: hemoglobin (Hb), ferritin, C-reactive proteins (CRP), alpha glycoprotein (AGP), serum Zn. Ferritin concentrations were adjusted for inflammation using Thurnham's correction factors. International cut-off points were used. The median age was 28 years. Of the women, 18.3% (116/633) had anemia and 18.3% (21/115) of them had Fe deficiency. Adjusting ferritin concentrations for inflammation, the proportion of anemic women with Fe deficiency increased to 22.6% (26/115), and Fe deficiency in the total sample varied from 7.5% (48/639) to 10.0%. (62/639). Serum Zn deficiency was high, 35.7% (234/654), 25.0% of women with Zn deficiency had anemia, with or without inflammation. 42.7% (273/641) women had inflammation. The results suggest an apparent association between anemia and Zn deficiency, a nutritional disorder little studied in Cuba. There is high concordance between the unadjusted and adjusted ferritin concentrations values for inflammation.

Keywords: Anemia, Zinc Deficiency, Women, Ferritin, Cuba

1. Introduction

The most common and widespread nutritional disorder on the planet is Fe deficiency. It has been estimated to cause approximately half of the cases of anemia in the world [1, 2], although other nutritional factors have also been associated with anemia, including Zn deficiency [3].

Approximately 17% of the world's population is considered to

be at risk of inadequate Zn intake, especially children and WRA. The prevalence of Zn deficiency is estimated to be among the most prevalent micronutrient deficiencies globally [2-5].

Various studies have found an association between Zn deficiency and anemia [3].

Although Zn deficiency is not a primary cause of anemia, it has been suggested that, through an indirect mechanism, it could affect the concentration of Hb and, as a consequence,

the prevalence of anemia. The mineral deficit favors the development of infections, which can cause systemic inflammation and this in turn decrease erythropoiesis [3].

In clinical and population studies, one of the most widely used biomarkers to assess anemia is hemoglobin concentration, however it is neither sensitive nor specific for estimating Fe deficiency [1, 3, 6, 7].

In order to estimate and evaluate Fe deficiency, various biomarkers have been used, including serum protein ferritin, which estimates iron stores [2, 6, 7, 9].

The recommended biomarker to estimate the nutritional status of Zn is serum Zn, however, like ferritin; its concentrations may be affected in the presence of systemic inflammation due to infection or other causes. Ferritin tends to increase [2, 6-9] and serum Zn decreases [2-5].

Which could lead to underestimate the deficiency of Fe deposits and overestimate the deficiency of serum Zn. In order to monitor the effect of inflammation on micronutrient biomarkers by different methods [2, 9].

It has been recommended, especially in population studies, to include the measurement of acute phase proteins of inflammation as biomarkers of this state, the CRP and AGP [2].

In Cuba, anemia continues being the main known specific nutritional deficiency problem, and it is estimated that Fe deficiency is the main factor with which it is associated [1, 4, 5, 7, 10]. There is little information from studies that have explored Zn deficiency in women with Fe deficiency and anemia [11].

Fe and Zn deficiencies and anemia have a significant negative impact on health and decrease the quality of life in women [3, 6, 7, 12].

It is intended to identify hematological manifestations of anemia, iron and zinc deficiency and its relationship with inflammation in WRA from different provinces of Cuba.

2. Materials and Experiments

A cross-sectional, descriptive-exploratory study, with a clinical approach, was carried out from 2016 to 2018. The selection of the sample of women was based on the design of a previous study carried out on children aged 6 to 59 months, stratified by region, from the eastern (Santiago de Cuba and Holguín), central (Sancti Spiritus and Cienfuegos) and Havana. From each province, 30% of the municipalities were chosen, including the municipal capital. Two-stage cluster sampling was performed using the primary care level structure. The health areas were the primary selection units and the family doctor's offices, the secondary units. A total of 1011 children were included, whose mothers were summoned to participate in the study. Not all the mothers came with their children (21), some had more than one child (75), others did not consent to participate in the study (14) and the women who did not respond were not replaced, the sample of women was reduced to 901.

Inclusion criteria: 18 to 40 years of age, apparent good health, without chronic inflammatory diseases and/or those that cause blood loss.

Exclusion criteria: One or more of the following criteria: pregnant, lactating, with the presence of known diseases that affect the metabolism of minerals, physical deformities, consumption of mineral supplements and/or medications that interfere with the metabolism of Zn and not attending fasting state.

By applying the criteria, 221 women were excluded from the study, the sample was reduced to 680 women. Of the sera, 23 were hemolyzed and 3 had Zn values above 160.9 µg/dL, a limit considered probable contamination [8], therefore, the final sample size was 654 women.

2.1. Procedures

Biochemical: determination of Hb in whole blood to diagnose anemia, serum ferritin to assess Fe deficiency, serum Zn to assess Zn nutritional status, serum CRP and AGP as biomarkers of inflammation.

Blood extraction was performed on women in a state of overnight fasting, by puncture of the antecubital vein, after disinfection of the area, and was performed by authorized and trained personnel who followed the recommendations for the processing of minerals in biological materials to prevent contamination. contamination [1]. On the same day of blood extraction, 1 mL of total blood with anticoagulant was taken to measure Hb and the remaining mL was used to obtain serum, by centrifugation at 14,000 rpm for 5 minutes. The serum was stored at -40°C until further analysis.

Serum Zn concentrations determination were made by trained personnel in the Nutritional Anemia and Metallic Contaminants Laboratories of the National Institute of Hygiene, Epidemiology and Microbiology (Inhem) and the Spectroscopy Laboratory of the Center for Chemical Bioactives, "Marta Abreu" Central University of Las Villas. Internal quality control was performed. The equipment was calibrated and certified. In both laboratories, a direct determination method was used, developed and optimized.

Hb was determined with an ABX Micros 60 hematology analyzer (Horiba, France). Ferritin and biomarkers of inflammation were determined by turbidimetric methods.

2.2. Data Collection and Analysis

A database was created. The SPSS 20.0 statistical package was used. The distribution of continuous quantitative variables was checked using simple graphic resources and a histogram was made. The continuous variables that showed positive asymmetry were described by means of the median, the 25th and 75th quartiles, the minimum and maximum values. Ferritin values were adjusted for inflammation, using the correction factors of Thurnham *et al* [9].

The statistics of the categorical variables were expressed using absolute numbers and percentages. The association between the categorical variables anemia, Zn deficiency and Fe deficiency was explored by calculating the odds ratio.

Ethical aspects: The study adhered to the principle of the Declaration of Helsinki [13].

Table 1 shows the study variables and cut-off points.

3. Results

The median age of the women was 28 years, the minimum age 18 and the maximum 40.

Table 1. Variables and categories.

Variable	Indicator	Cut-off point
Zinc [4]	Serum Zn (µg/dL)	< 70
Anemia [1]	Hemoglobin (g/L)	Yes: < 120 Severe < 80
Severity of anemia [1]	Hemoglobin (g/L)	Moderate 80–109 Mild 110–119
Iron deposits [1]	Ferritin (µg/L)	< 15
Inflammation	C reactive protein (mg/L)	> 5 [1]
	Alpha glycoprotein (g/L)	> 1 [1]

Table 2 shows the parameters that describe the biochemical variables.

Missing data on some variables, not representing an apparent risk of bias in the calculation of descriptive statistics or measures of association, were due to blood coagulation or insufficient serum.

Table 2. Biochemical parameters of women of reproductive age from different provinces, Cuba.

Variables	Min.	Max.	P25	Median	P75
Hb (g/L) (n=633)	64,00	154,00	123,00	130,00	136,00
Ferritin (µg/L) (n= 641)	5,2	1260,4	29,6	54,2	84,7
Ferritin _{adj} * (µg/L) (n= 641)	5,2	1260,4	26,2	44,4	70,4
Serum Zn (µg/dL) (n=654)	31,7	151,2	65,4	75,7	87,2
CRP (mg/L) (n=641)	0,1	86,8	1,1	2,3	6,4
AGP (g/L) (n=641)	0,2	2,9	0,64	0,8	1,0

Hb: hemoglobin, ferritin_{adj}: inflammatory-adjusted ferritin, Zn: zinc, CRP: C-reactive protein, AGP: Alpha glycoprotein.

As seen in Table 3, 25% of Zn-deficient women had anemia, with and without inflammation. The inflammation condition does not seem to modify the relationship between anemia and Zn deficiency.

Table 3. Anemia and Zn deficiency according to the presence or absence of inflammation.

Inflammation			Anemia		Total
			No	Yes	
No	Zn deficiency	no	191 (84,1%)	36 (15,9%)	227 (100%)
		yes	97 (75,2%)	32 (24,8%)	129 (100%)
		Total	288 (80,9%)	68 (19,1%)	356 (100%)
Yes	Zn deficiency	no	151 (87,3%)	22 (12,7%)	173 (100%)
		yes	74 (74,7%)	25 (25,3%)	99 (100%)
		Total	225 (82,7%)	47 (17,3%)	272 (100%)
Zn evaluation		No deficient	342 (85,5%)	58 (14,5%)	400 (100%)
		Deficient	171 (75,0%)	57 (25,0%)	228 (100%)
		Total	513 (81,7%)	115 (18,3%)	628 (100%)

Risk stimation					
Inflammation		Value	Confidence Interval at 95%		
			Lower	Upper	
No	Odds ratio	1,7	1,0	2,9	
	N	356			
Yes	Odds ratio	2,3	1,2	4,4	
	N	272			
Total	Odds ratio	1,9	1,3	2,9	
	N	628			

Figure 1 shows the percentages of women with anemia and depletion of Fe deposits evaluated by unadjusted ferritin concentrations and adjusted for inflammation, when stratifying Fe deficiency by inflammation. The proportion of

Anemia was diagnosed in 18.3% (116/633) of women, of which 18.3% (21/115) had decreased Fe deposits. Mild anemia prevailed in 15.0% (95/633). When adjusting ferritin concentrations for inflammation, the proportion of anemic women with iron deficiency increased to 22.6% (26/115) and in the total sample iron deficiency varied from 7.5% (48/639) to 10.0% (62/639). The kappa index (0.068) showed good agreement between the percentages of decrease in Fe deposits with adjusted and unadjusted ferritin concentrations.

The decrease in serum Zn in the sample was 3.6 times higher than the depletion of Fe deposits, 35.7% (234/654). Approximately half of the women with anemia had decreased serum Zn 49.1% (57/116).

The proportion of women with inflammation was 42.6% (273/641), due to increased CRP 31.7% (203/641) and AGP 25.1% (161/641).

The risk of Zn deficiency anemia was measured, in the absence and presence of inflammation.

women who were anemic and Fe depleted as measured by unadjusted and adjusted ferritin varied by 5.3 percentage points, from 21.4% (3/14) to 26.7% (8/30).

The risk of anemia associated with the deficiency of Fe

deposits (estimated by ferritin concentrations not adjusted for inflammation and adjusted), seems to be influenced by inflammation. With unadjusted ferritin concentrations and without inflammation ($n=355$), the $OR=7.0$ (95% CI 3.2-15.0) and with inflammation ($n=272$), the $OR=1.3$ (95% CI 0.3 -4.9). The total value ($n=627$) of $OR=4.3$ (95% CI 2.3-8.0). With adjusted ferritin and without inflammation ($n=355$), $OR=7.0$ (95% CI 3.2-15.0), with inflammation ($n=272$) $OR=1.8$ (95% CI 0.7-4, 5), the total value ($n=627$) of $OR=3.8$ (95% CI 2.2-6.7).

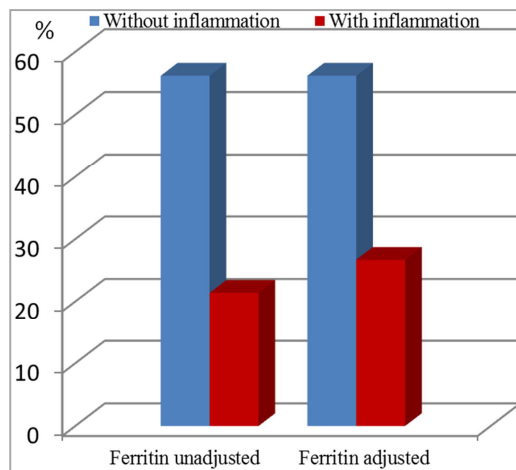


Figure 1. Anemia and decreased iron stores.

4. Discussion

One of the starting conjectures of the present study was corroborated when diagnosing low serum Zn in women. The results confirm that in the group there is more than one nutritional factor associated with anemia, depletion of Fe deposits and decreased serum Zn.

Deficiency in Fe deposits was previously reported in WRA [6]. In a group vulnerable to Fe deficiency, it is very likely that Zn deficiency also exists, especially if both deficiencies are influenced by nutritional factors. Zn and Fe are similarly distributed in foods [4].

The proportion of women diagnosed with anemia is in correspondence with the characteristics of the distribution of this health problem in Cuba [6]. The proportion of anemic women with decreased serum Zn and Fe depletion is consistent with reports from overseas studies in women of the same age group [3, 14].

In the course of inflammation, serum Zn penetrates the liver, and its concentration tends to decrease [2]. In the sample studied, the decrease in serum Zn does not seem to be associated with inflammation. Similar results have been found in previous studies [7, 8]. Zn homeostasis during inflammation in WRA might be modulated by the hormonal environment. In any case, it remains to be clarified how inflammation influences Zn status.

Various investigations have reported an association between anemia, Fe deficiency and inflammation [6, 7, 9, 15]. Ferritin is an acute phase protein, whose function is related to the storage

of iron in cells, it is released into the blood in response to an inflammatory stimulus, so it can be detected increased in blood even when iron stores are depleted [2, 3, 6, 7, 9].

With the correction factors used to adjust ferritin for inflammation, a difference in Fe deposits was detected, although to a lesser extent than previously reported [6, 9]. This methodology has been used mainly in population studies.

The results of the study may constitute an alert, the proportion of women with decreased serum Zn exceeded the value of 20%, cut-off point proposed by experts to consider a population at risk of micronutrient deficiency [4], however the study did not had a population focus.

Serum Zn is not a good biomarker of Zn deficiency in the body, it does not detect mild states of deficiency [2, 4], so the true deficiency of the mineral could have been underestimated in the group.

It is recommended to implement further research that allows deepening the knowledge of the relationship between anemia and Zn deficiency as well as the factors that could be causing the deficiency of the micronutrient in the group of women of reproductive age, which would contribute to the eradication of both health disorders.

5. Conclusion

Decreased serum Zn, Fe deposits estimated by serum ferritin, and anemia were identified in healthy women. The results suggest an apparent association between anemia and zinc deficiency, a nutritional disorder little studied in Cuba. The inflammation condition does not seem to modify the relationship between anemia and Zn deficiency. There is good agreement between the percentages of decrease in Fe depletion with adjusted and unadjusted ferritin. The risk of anemia associated with deficiency of Fe stores appears to be influenced by inflammation.

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References

- [1] World Health Organization. (2011). Haemoglobin concentrations for the diagnosis of anemia and assessment of severity. Vitamin and Mineral Nutrition Information System (VMNIS). Geneva: World Health Organization.
- [2] Raiten DJ, Sakr Ashour FA, Ross C, Meydani SN, Dawson HD, Stephensen CB et al. (2015). Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence (INSPIRE). *The Journal of Nutrition*, 145 (5), 1039S–1108S. doi: 10.3945/jn.114.194571.
- [3] Greffeuille V, Fortin S, Gibson R, Rohner F, Williams A, Young MF, et al. (2021). Associations between Zinc and Hemoglobin Concentrations in Preschool Children and Women of Reproductive Age: An Analysis of Representative Survey Data from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The Journal of Nutrition*, 151 (5), 1277–1285. doi: 10.1093/jn/nxaa444.
- [4] International Zinc Nutrition Consultative Group (IZiNCG). (2004). Assessment of the Risk of Zinc Deficiency in Populations and Options for Its Control. Technical Document # 1. *Food Nutrition Bulletin*, 25 (1 Suppl 2), S99–S203.
- [5] Hess SY. (2017). National Risk of Zinc Deficiency as Estimated by National Surveys. *Food and Nutrition Bulletin*, 38 (1), 3–17. doi: 10.1177/0379572116689000.
- [6] Pita Rodríguez GM, BasabeTuero B, Díaz Sánchez ME, Gómez Álvarez AM, Campos Hernández D, ArochaOriol C, et al. (2017). Anaemia and Iron Deficiency Related to Inflammation, *Helicobacter pylori* Infection and Adiposity in Reproductive-age Cuban Women. *Medic Review*, 19 (2–3), 10–17. doi: 10.37757/MR2017.V19.N2-3.3.
- [7] Wirth JP, Woodruff BA, Engle-Stone R, Namaste S ML, Temple VJ, Petry N et al. (2017). Predictors of anemia in women of reproductive age: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The American Journal of Clinical Nutrition*, 106 (Suppl 1), 416S–427S. doi: 10.3945/ajcn.116.143073.
- [8] McDonald CM, Suchdev PS, Krebs NF, Y Hess S, Wessells KR, Ismaili S et al. (2020). Adjusting plasma or serum zinc concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The American Journal of Clinical Nutrition*, 111 (4): s927–937. doi: 10.1093/ajcn/nqz304.
- [9] Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. (2010). Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. *The American Journal of Clinical Nutrition*, 92 (3), 546–55. doi: 10.3945/ajcn.2010.29284.
- [10] Pita Rodríguez GM, Chávez-Chong C, Lambert-Lamazares B, Montero-Díaz M, Selgas-Lizano R, Basabe-Tuero B et al. (2021). Influence of Inflammation on Assessing Iron-Deficiency Anemia in Cuban Preschool Children. *Meddic Review*, 23 (3–4), 37–45. doi: 10.37757/MR2021.V23.N3.7.
- [11] Gómez Álvarez AM, Pita Rodríguez GM, GarcíaPino C, Bacallao Gallestey J, Ordás González Arletys, Cardellá Rosales L et al. (2020). Deficiencia de Zinc en Mujeres de Edad Reproductiva, Cuba. Zinc Deficiency in Age Reproductive Women, Cuba. *Revista Cubana de Salud Publica*, 46 (4), e2224.
- [12] Cook RL, O'Dwyer NJ, Parker HM, Donges CE, Cheng HL, Katharine S. (2017). Iron Deficiency Anemia, Not Iron Deficiency, Is Associated with Reduced Attention in Healthy Young Women. *Nutrient*, 9, 1216. Doi: 10.3390/nu9111216.
- [13] Declaration of Helsinki of the World Medical Association. (2013). Ethical principles for medical research in human beings. 64th General Assembly, Fortaleza. *Etices Bulletin of Bioethics*, 5 (4), 9p.
- [14] Holmes JB, Kroeun H, Houghton LA, Gibson RS, Harding KB, De-Regil LM et al. (2019). Including 60 mg Elemental Iron in a Multiple Micronutrient Supplement Blunts the Increase in Serum Zinc after 12 Weeks of Daily Supplementation in predominantly Anemic, Nonpregnant Cambodian Women of Reproductive Age. *The Journal of Nutrition*, 149 (9), 1503–1510. doi: 10.1093/jn/nxz097.
- [15] Merrill RD, Burke RM, Northrop-Clewes CA, Rayco-Solon P, Flores-Ayala R, Namaste SML. (2017). Factors associated with inflammation in preschool children and women of reproductive age: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The American Journal of Clinical Nutrition*, 106 (Suppl 1): 348S–358S. doi: 10.3945/ajcn.116.142315.