

Differences in the hemoglobin cut-off point for the diagnosis of anemia as a function of race/color

Diferenças no ponto de corte de hemoglobina para diagnóstico de anemia em função da raça/cor

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ABSTRACT

Hemoglobin levels vary according to age, gender, different phases of pregnancy, smoking habit, and altitude. In the early 90s, researchers began to notice unexplained differences in hemoglobin levels between whites and blacks in various age groups. Since then, studies began to be published to identify which factors would be responsible for such differences. From a review of the literature, we aimed at exposing relevant aspects that may assist in the understanding of why blacks have lower levels of hemoglobin in relation to whites. The Medline, Lilacs, and Pubmed databases were used for this review. Studies have shown that the levels of hemoglobin in blacks are lower, ranging between 0.5 and 1 g/dL in relation to whites. This difference remains, even controlling for possible confounding factors such as intake and iron nutritional status, socioeconomic status, age, and comorbidities among others. The studies, however, do not come to a conclusion about what raises this difference between races. Therefore, proposing specific cut-off points as a function of race, as some authors suggest, may be precipitated and result in not identifying people with anemia, which is considered a serious public health problem in Brazil.

Key words: Anemia/diagnosis; Nutritional Anemias/diagnosis; Ethnicity and Health; Hemoglobinopathies.

RESUMO

Os níveis de hemoglobina variam em função de idade, sexo, diferentes fases da gestação, hábito de fumar e altitude. No início dos anos 90, pesquisadores começaram a observar diferença inexplicável nos níveis de hemoglobina entre brancos e negros nas mais diversas faixas etárias. A partir de então, estudos começaram a ser publicados a fim de identificar quais possíveis fatores seriam responsáveis por tais diferenças. Objetivou-se, a partir de uma revisão de literatura, expor aspectos relevantes que possam auxiliar no conhecimento sobre por que negros possuem menores níveis de hemoglobina em relação aos brancos. A base de dados utilizada para tal revisão foi Medline, Lilacs e Pubmed. Estudos têm evidenciado que os níveis de hemoglobina em negros são menores, variando entre 0,5 e 1g/dL em relação à raça branca. Essa diferença permanece, mesmo controlando possíveis fatores de confusão como ingestão e estado nutricional de ferro, nível socioeconômico, idade, comorbidades, entre outros. Os estudos, entretanto, não chegam a uma conclusão sobre o que realmente gera essa diferença entre as raças. Assim, propor pontos de corte específicos em função da raça, como alguns autores sugerem, pode ser precipitado e ter como consequência a não identificação de portadores de anemia, que é considerada sério problema de saúde pública no Brasil.

Palavras-chave: Anemia/diagnóstico; Anemias Nutricionais/diagnóstico; Origem Étnica e Saúde; Hemoglobinopatias.

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INTRODUCTION

According to the World Health Organization (WHO), nutritional anemia is defined as the condition in which the concentration of hemoglobin is below values considered normal due to the lack of one or more essential nutrients, irrespective of the origin of this lack. Iron deficiency anemia is characterized when the reduction in hemoglobin concentration is the consequence of iron deficiency.^{1,2}

Iron deficiency is the most prevalent isolated nutritional deficiency in the world and the leading cause of nutritional anemia, especially in developing countries. Some groups are considered at risk for iron deficiency, children among them, especially infants and preschoolers, teenagers, women of childbearing age, and pregnant women.³

Considered a serious public health problem, anemia compromises the psychomotor development, reduces resistance to infections, and may increase maternal and child morbidity and mortality. In Brazil, regional studies show prevalences of iron deficiency anemia ranging from 30-70%.³⁻⁵ According to the WHO, anemia prevalence above 40% is considered a disease of serious public health concerns in a particular population, and may be expected to reach up to 100%.^{1,6} The prevalence of anemia was 65% in a nationwide study conducted in 2004 with children between six and 12 months old; the South-eastern region presented the highest prevalence (70.4%).⁵ Data from Brazilian studies show that the prevalence of anemia reaches 15 to 60% in pregnant women, around 20% of women of childbearing age, and 20% in adolescents.^{6,7}

Some authors, in addition to evaluating anemia, also analyzed the nutritional status of iron. Because iron deficiency occurs gradually and progressively in the body, learning about the biochemical parameters that alter before hemoglobin reduction helps adopting measures to prevent anemia.^{7,8}

Some parameters that can be used to indicate iron depletion in the body are: serum ferritin, transferrin saturation, free erythrocyte protoporphyrin and, more recently, dosing of transferrin receptors has been used.⁸ Ideally, these parameters should not be used in isolation because factors such as infection, neoplasms, liver diseases, alcohol intake, and use of certain medications can interfere with their values and lead to hasty conclusions.⁸

It is known that hemoglobin levels vary according to age, gender, different stages of pregnancy, smoking

habit, and altitude. Therefore, these factors should be considered in the diagnosis of iron deficiency anemia.^{1,7} In the 90s, researchers began to notice unexplained differences in hemoglobin levels between whites and blacks.^{9,10}

Since then, studies began to identify low levels of hemoglobin and hematocrit in blacks. From there, questions have emerged to try and explain this difference. Factors such as socio-economic issues, differences in nutritional status or iron intake, genetic issues, and/or comorbidities have been identified.^{9,10} Thus, this article, by means of a literature review, exposes relevant aspects that may assist in the identification of factors responsible for the difference between the levels of hemoglobin in whites and blacks, as well as to conclude if the adoption of a specific cut-off point for the diagnosis of anemia based on race is needed.

METHODOLOGY

In this review, articles indexed in the databases MedLine, PubMed, Scientific Electronic Library Online (SciELO-Brazil), and Latin American literature and Caribbean Health Sciences (LILACS), published in Portuguese and English between 1994 and 2009, were evaluated. Articles published prior to 1994 that were relevant to the subject and cited in the articles previously selected were also included.

The descriptors used, with their words in Portuguese and English, were: iron deficiency anemia; iron deficiency; race; hemoglobin. The survey was conducted by combining these terms or using them in isolation.

The inclusion criteria were: articles available in full, which evaluated the prevalence of iron deficiency anemia in samples where it was possible to analyze differences between races (whites and blacks).

In addition, documents from government institutions addressing the theme "anemia", such as the World Health Organization (WHO) and Ministry of Health, were consulted. Book chapters that could aid in the discussion of the theme were also consulted.

RESULTS

A total of 52 articles were found in the search conducted in MedLine and PubMed. Of these, 15 were selected from their titles according to the inclusion criteria. Eight articles were found in the survey con-

ducted in SciELO Brazil, and two were selected. Five articles pertaining to the topic were found in Lilacs; two did not fit the inclusion criteria and three had already been selected in SciELO-Brazil.

The full reading of 17 articles was conducted; however, only eight were relevant and could contribute to the topic for this review.

DISCUSSION

Studies have shown a difference from 0.5 to 1 g/dL in hemoglobin levels between whites and blacks even after controlling possible confounding factors such as: iron intake and nutritional status, socioeconomic status, age, and comorbidities among others.⁹⁻¹¹ For researchers, whether that difference would be due to racial characteristics, genetic factors, hemoglobinopathies (such as sickle cell anemia and thalassemias), which are more prevalent in the black population, social and environmental factors, or a combination of these factors is still not clear.⁹

Dallman et al.¹² evaluated children and adolescents (1,718 whites and 741 blacks) of both genders, aged between five and 14 years, belonging to the middle-class. Those who presented some type of hemoglobinopathy through hemoglobin electrophoresis were excluded. A difference of 0.5 g/dL was detected in hemoglobin levels in both genders. The authors indicated that values for hemoglobin levels considered normal were lower in black individuals. However, they recommended further studies to identify the specific factors that could account for this difference.

Some hemoglobinopathies are most prevalent in the black population and should be considered in studies that seek answers to these differences in hemoglobin levels between races, as, for example, sickle cell anemia is the most prevalent hereditary disease in Brazil¹³. Hemoglobin S in homozygosity or combination with some other hemoglobins causes red blood cells to acquire the shape of half-moon or sickle.^{13,14}

Sickle-cell anemia has a high prevalence in several countries in Africa and, consequently, due to the slave trade and, more recently, spontaneous emigration, in afro-descent populations. The highest incidence of the S gene in Africa originated from the relative protective effect of the sickle cell trait against severe forms of malaria caused by *Plasmodium falciparum*.^{14,15}

Thalassemia is another important hemoglobinopathy. It results from a reduction in the rate of synthesis

of one of the globin chains that make up hemoglobin.¹⁵⁻¹⁷ Both iron deficiency anemia and thalassemia cause reduction in hemoglobin levels, microcytosis, and hypochromia, however, the transferrin saturation is invariably high in thalassemia, which is a useful differential parameter.¹⁸

Thus, none of these hemoglobinopathies (sickle cell anemia or thalassemia) can explain the low levels of hemoglobin in blacks. However, Beutler and West¹⁹, when assessing the effect of thalassemia and sickle cell anemia on the prevalence of anemia among white and black Americans, found that, when individuals with these hemoglobinopathies were removed from the sample, the prevalence of anemia was reduced but remained higher in blacks than whites. The authors concluded that there may be another genetic factor responsible for this difference, not yet studied. Thus, in this study, the existence of any hemoglobinopathy did not explain why blacks showed a higher prevalence of anemia than whites.

Even if sickle cell anemia and thalassemias are not responsible for the difference found in hemoglobin levels between whites and blacks, hemoglobinopathies should be investigated, especially in cases where there is no positive response to treatment with ferrous sulphate. According to Santana et al.²⁰, 16% of children referred to the Pediatric Hematology Service of the General Hospital of the Federal University of Minas Gerais (UFMG), due to poor response to treatment with oral iron, are diagnosed with β -thalassemia.

INFLUENCE OF IRON INTAKE AND SOCIOECONOMIC FACTORS

Perry et al.²¹ concluded that the low levels of hemoglobin found in black Americans did not result from nutritional factors, such as iron intake or nutritional status. The authors worked with a sub-sample of the National Health and Nutrition Examination Survey (NHANES II). Biochemical data were collected from 5,157 people. Among these, teenagers were excluded due to the difficulty of controlling physiological alterations resulting from sexual maturation and adults over 45 years were also excluded due to the high probability of chronic inflammatory disease that could interfere with results. Individuals with some type of hemoglobinopathy were also excluded. The final sample was composed of 2,414 individuals,

including 381 blacks. The daily intake of iron was estimated based on a 24 hours feeding record.

The authors found that the hemoglobin levels were lower in blacks than in whites and this difference ($p < 0.05$) was of 0.84 g/dL in men, 0.55 g/dL in women, and 0.65 g/dL in children between three and 12 years old. No statistically significant difference was found between blacks and whites in serum ferritin, transferrin saturation, erythrocyte protoporphyrin, and iron intake. The authors suggested additional studies to elucidate the factors that could explain these differences between races.

Some questions should be considered in relation to the methodology of this study. First, a single 24 h feeding record was used to assess iron intake. The application of this type of record does not provide information on the average intake, therefore, it is not possible to consider this iron intake as reflecting the usual consumption by these individuals because it may reflect an atypical day in which this micronutrient was consumed in excess.

Some disadvantages are also inherent to the method such as the need to resort to the memory of individuals who often do not remember the size of portions consumed. The technique of using records requires trained individuals who can recall the real information from the previous food consumption. Another important point relates to sample size including blacks. Most studies seeking explanations for differences in the level of hemoglobin show a representative sample size for white individuals and small for blacks, which hamper the extrapolation of results.

Fabian et al.²² evaluated 312 women between 20 and 60 years old, residents of the city of São Leopoldo, Rio Grande do Sul. The prevalence of anemia was 19.8%. The difference in levels of hemoglobin was 0.8 g/dL between whites and blacks. In this study, black women showed three times higher risk of having anemia than whites. However, the sample had only 13 black women. Thus, this result should be interpreted with caution. As the authors themselves acknowledge, the sampling procedure aimed to proportionally represent the local population, but with the possibility of a random error because the sample size was determined to estimate the prevalence and not to investigate associations. The authors conclude that there is a need for more studies on the determinants of anemia, especially in black women.

In the National Survey of Demography and Health (PNDS),²³ the prevalence of anemia in women of childbearing age was nearly 30%. Such prevalence

was nearly six times higher among black women. This difference was also recorded for children; the prevalence of anemia is also higher in black children.

This same study revealed an important data that must be considered in this discussion. Food security conditions and the varying degrees of food insecurity by using the Brazilian Scale of Food Insecurity (EBIA), validated for the Brazilian reality between 2003 and 2004, were evaluated. The results underscored that in households where black women lived, the prevalence of severe food insecurity is twice higher than in those where white women are residing²³. This reinforces the importance of, in studies that seek to evaluate the differences between the levels of hemoglobin in different races, to consider social factors because the influence of socioeconomic indicators on nutrition and, consequently, installation of conditions such as iron deficiency anemia are well known.

Unfortunately, this was not the goal of the PNDS²³ and the question posed is whether the higher prevalence of anemia found in black children and women correlates with the worst indicators of food security, also found at homes where black women resided. Possibly, such a situation of food insecurity affects not only iron intake but also that of other micronutrients such as vitamin A: the prevalence of hypovitaminosis A was also higher in black women and children.

Assunção et al.²⁴ evaluated children from zero to five years of age in Pelotas-RS and showed that the prevalence of anemia was higher ($p < 0.006$) in children who were not white, however, the authors did not discuss whether these differences would be on the basis of race because this was not objective of their study.

Another study, also conducted in Pelotas-RS with 362 children under six years of age and assisted by the Pastoral da Criança, found 29% higher risk ($p = 0.02$) of non-white children to have anemia.²⁵ Something to be considered in these studies is the adoption of the cut-off values of hemoglobin proposed by WHO¹ (< 11 g/dL). Therefore, if the observed differences between races are due to genetic factors, the prevalence of anemia found in the studies, always higher in the black population, is overestimated.

The search for factors responsible for lower values of hemoglobin and hematocrit found in blacks is also required in order to guide the development of intervention measures.

Knowing that such measures are based on results of population studies, once determined that such differences would be due to social issues, the need to im-

plement targeted policies in this racial group becomes clear. Otherwise, if it is proven that these differences are due to inborn genetic processes, spending on social programs and indication for treatment with ferrous sulphate will be unnecessary. If there is a genetic factor, individuals may be subjected to treatments that will not bring satisfactory results because these biochemical alterations would have no relationship with iron intake.

Table 1 summarizes the studies discussed in this article. Values of differences between whites and blacks and the studied age group are presented. One can see that the interest in answering that question has been going for a few years in studies in different age groups.

According to Table 1, the differences ranged between 0.4 and 0.84 g/dL. They were identified in different age groups (children, adolescents, adults, and elders) and both genders. This suggests that the lower levels of hemoglobin in black individuals are due to some factor or variable that is present in both genders and different age groups.

Zakai et al.²⁶ evaluated 19,836 Americans of both genders. They used a multivariate model to evaluate the potential causes of the differences found in hemoglobin levels between races. The authors considered as variables: demographics (age, gender), socioeco-

nomics (education level, income), and associated comorbidities (high blood pressure, kidney disease, diabetes, excess weight), and investigated inflammation through the analysis of the C-reactive protein (CRP).

The prevalence of anemia found was three times higher in blacks; however, none of the studied variables, after all statistical adjustments, was able to explain this difference. The authors proposed further studies with more variables to try to explain the results. Other factors that could have been assessed would be iron consumption and nutritional status (ferritin and transferrin saturation among others). This should always be considered in these studies in order to determine if there is no difference between iron consumption and iron nutritional status in blacks and whites.

SPECIFIC CUT-OFF POINTS ACCORDING TO RACE

It is known that hemoglobin levels vary according to gender, age, stages of pregnancy, altitude, and smoking habit. In these cases, specific cut-off points that are considered normal variations can be adopted.^{27,28}

Table 1 - Summary of studies that found significant differences ($p < 0.05$) in hemoglobin levels between whites and blacks, in different age groups

Study	Age group (years)	Gender	Average of hemoglobin values g/dL		Difference found g/dL
			Black	White	
Dalman <i>et al.</i> ¹²	5-9	F	12.5	12.9	0.4
		M	12.6	13.0	0.4
	10-14	F	12.9	13.4	0.5
		M	13.1	13.7	0.6
Perry <i>et al.</i> ²¹	3-12	F/M	12.03	12.68	0.65
	18-45	F	12.84	13.39	0.55
		M	14.48	15.32	0.84
Johnson-Spear ³⁰	18-44	F	12.6	13.4	0.8
Beutler & West ¹⁹	20-60	F	12.7	13.49	0.79
		M	14.45	14.93	0.48
Fabian <i>et al.</i> ²²	20-60	F	12.0	12.8	0.8
Patel <i>et al.</i> ³¹	71-82	F	12.8	13.5	0.7
		M	13.6	14.4	0.8
Dalman <i>et al.</i> ³²	3-11	F/M	12.15	12.73	0.58
	18-44	F	12.8	13.6	0.8
		M	14.5	15.3	0.8
Zakai <i>et al.</i> ²⁶	> 45	F	12.7	13.5	0.8
		M	14.0	14.8	0.8

As there seems to be a difference in the concentration of hemoglobin between whites and blacks, the chance of using specific cut-off points for the diagnosis of anemia on the basis of race is hypothesized.^{10-12,29}

Johnson-Spear and Yip³⁰ evaluated the need for adopting a race-specific criterion for screening iron deficiency. Their analysis of data from white and black women who participated in the National Health and Nutrition Examination Survey (NHANES II) suggests the following parameters for the diagnosis of iron deficiency: transferrin saturation, mean corpuscular volume, and erythrocyte protoporphyrin. The socioeconomic status was defined based on educational level and income.

The authors calculated sensitivity and specificity using different cut-off points to define what would be the best for screening iron deficiency. The results showed that black women had lower levels of hemoglobin than white women and that these differences do not change after statistical adjustments depending on the socioeconomic status and iron deficiency.

The concentration of hemoglobin with higher sensitivity and specificity to detect iron deficiency in white women was 13 g/dL and 12 g/dL in black women. It is worth mentioning that the use of hemoglobin for the screening of individuals with iron deficiency will identify those with severe disabilities; in cases where there is intermediate deficiency, the use of other parameters, such as serum ferritin would be interesting.

The authors concluded that there is a need to adopt specific cut-off points on the basis of race because this ensures a better prediction of risk for iron deficiency at both individual and population level.

The adoption of specific cut-off points on the basis of race/color should be examined with caution. None of the studies that sought to identify which variables could explain the differences found in the hemoglobin levels between whites and blacks was able to answer this question, i.e. the factor responsible for this difference has not yet been identified. In reality, if there is no relationship between social aspects and lower hemoglobin levels observed in the black population, the adoption of specific cut-off points could be justified because that difference would probably be due to genetic and racial issues.

Otherwise, if the social factor has a participation in this difference, it is not justifiable to adopt lower cut-off points for blacks because the prevalence of anemia would be underestimated and part of the population would be getting false diagnoses.

Even assuming that there is a genetic issue involved, it would not be appropriate to say that all or most of blacks are carriers of this possible mutation. Therefore, the adoption of lower cut-off points would not identify those cases in which lower levels of hemoglobin are arising from the inadequate iron intake or of adverse social conditions.

Reeves et al.⁹ stand in favor of the use of uniform cut-off points, regardless of race/color, for populations with high prevalence of anemia. To those populations where anemia does not represent a risk, the authors are in favor of specific cut-off points, depending on race/color. However, this is very complicated because if every locality adopts different cut-off points, the prevalence of anemia, of course, will be different among regions and this will make it harder for the government to identify those who require more investments.

CONCLUSION

It can be concluded that the reviewed studies accuse difference in hemoglobin concentration and prevalence of anemia between whites and blacks. This difference, however, remains unexplained, at least by the studies evaluated here. None of them fully showed what would be the factor responsible for these differences; they only discarded variables that could account for this difference. Therefore, it is too early to recommend changes in cut-off points and the adoption of specific criteria for race/color. Until reasons why blacks present hemoglobin levels lower than whites are determined, there are no sufficient arguments to justify changing the diagnostic criteria for anemia, mainly because this disease is considered a public health problem in Brazil.

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