PERSPECTIVE

Appropriateness of Hemoglobin Cut Off's for Defining Anemia

Radhika Kapil

Chief Resident, Department of Pathology, Jawaharlal Nehru Medical College, Belgaum, Karnataka

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Corresponding Author

Address for Correspondence: Dr. Radhika Kapil, Chief Resident, Department of Pathology, Jawaharlal Nehru Medical College, Belgaum, Karnataka

E Mail ID: drradhikapatho@gmail.com

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Background

The use of the hemoglobin cut-off points permits the identification of populations at greatest risk of anemia. The reference cut off's of Hb also facilitates the monitoring and assessment of progress towards preventing and controlling iron deficiency. These cut off's also provides the scientific basis for advocacy for the prevention of anemia. There has been continued discussion about the appropriateness of the Cut Off's used to define anaemia and their applicability to different populations, which has implications for epidemiological surveillance, monitoring, and targeting (1,2).

Haemoglobin concentration is affected by physiological characteristics such as age, sex, and pregnancy status, as well as environmental factors such as smoking and altitude. Several studies have shown that the population distribution of haemoglobin is lower in black people than in white people (1,3,4). Only a few studies from low-income and middle-income countries have, however, examined the applicability of the WHO cut off's to other populations (4,5).

The haemoglobin cut-offs presented in Table-1 are used to diagnose anaemia in individuals in a screening or clinical setting.

Evolution of Haemoglobin Cut Off's

The scientific basis for current WHO cut offs of haemoglobin to define anemia which are found in literature are based on scientific data from the 1950's and 1960's (6,7,8,9,). These were consolidated in to a WHO publication of 1968 (10). The thresholds for mild, moderate, and severe anemia were published subsequently in WHO publication in 1989 (11). The overall anemia cut-offs have remained unchanged since 1968, with the exception that the original age group of children 5-14 years of age was split, and a cut-off of 5 g/l lower was applied to children 5-11 years of age (12).

The current WHO Cut-offs have been validated by findings among participants in the Second National Health and Nutrition Examination Survey (NHANES II) who were unlikely to have iron deficiency based on a number of additional biochemical tests. WHO in collaboration with UNICEF and United Nations University (UNU) reviewed NHANES II data to make adjustments in Hb cut off's for altitude and smoking (12,13).

The references that are given to 1968 WHO document were choice of numbers, in general. The surveys of the relatively small number of subjects, without documentation of methodology, and without efforts being made to remove patients with anemia in calculating the values. To further put these studies into the context of the times, the dilution of blood, sometimes obtained by finger puncture, was carried out with pipettes that were often inaccurate. Cyanmethemoglobin standards were not widely available, and calibration required oxygenation of a blood sample to serve as a standard with measurement of the amount of oxygen released by acid in a van Slyke apparatus. Needless to say, this procedure was not always carried out, and, as a consequence, results were often unreliable. In view of these difficulties, the WHO standard which are currently used need more strong data base (14).

Haemoglobin Cut Off's for Pregnant Mothers

The haemoglobin cut-off of 110 g/l for pregnant women was first developed in 1968 (6). In healthy, iron-sufficient women, haemoglobin concentrations change during pregnancy to accommodate the increasing maternal blood volume and the iron needs of the fetus. Hb concentrations decline during the first trimester, reaching their lowest point in the second trimester, and begin to rise again in the third trimester. Currently, there are no WHO recommendations on the use of different haemoglobin cut-off points for anaemia by trimester during pregnancy. It is recognized that during the second trimester of pregnancy, haemoglobin concentrations diminish approximately 5g/l.

For women, a hemoglobin concentration >170 g/L can perhaps be regarded as a moderately elevated value. During pregnancy, the upper level for defining high hemoglobin would be lower than that in non-pregnant women because of the physiologic changes in the hemoglobin concentration during pregnancy. The elevated hemoglobin concentration and the probability of association with adverse events depend on the specific individual or population under study.

Elevated Hemoglobin Concentration

Residence at high altitude above sea level and smoking are known to increase haemoglobin concentrations. Consequently, the prevalence of anaemia may be under estimated in persons residing at high altitudes and among smokers if the standard anaemia cut-offs are applied. (12) The Table-2 presents the recommended adjustments to be made to the measured haemoglobin concentration among persons living at altitudes higher than 1000 metres above sea level, Table-3 presents these adjustments for smokers. These adjustments must be made to the measured haemoglobin concentration for the anaemia cut-offs presented in Table 1 to be valid.

Elevation adjustments and smoking adjustments both are additive i.e. smokers living at higher altitudes would have two adjustments made.

An elevated hemoglobin concentration is usually the result of two mechanisms: increased red blood cell production as a compensatory mechanism when blood oxygen carrying capacity is compromised to meet the demand of tissue (with a net increase in red cell mass), or contracted plasma volume resulting in an appearance of greater red cell volume (without a net increase in red cell mass). One of the two most common non-pathologic reasons for elevated hemoglobin or red cell mass is residence at a higher altitude, where ambient oxygen concentration is lower. The other is cigarette smoking, which causes part of the hemoglobin to become non-functional as a result of binding with carbon monoxide. Respiratory and cyanotic cardiac conditions, which compromise proper oxygenation of blood, are the principal pathologic reasons for elevated hemoglobin concentration. The only condition of elevated hemoglobin that is due to the production of defective red blood cells, but not subject to the control of tissue oxygen drive, is polycythemia vera. This condition of increased red blood cell production share the one basic feature of increased red cell mass with normal or increased total blood volume.

There is also evidence of a genetic influence. In the United States, for example, individuals of African extraction have haemoglobin values 5 to 10 g/l lower than do those of European origin. This contrast is not related to iron deficiency (15).

Methods of Assessment of Haemoglobin

The method of haemoglobin measurement and blood sample source (capillary versus venous blood) both can affect the measured haemoglobin concentration. The cyanmethemoglobin and the HemoCue® system are the methods generally recommended for use in surveys to determine the population prevalence of anaemia. The cyanmethemoglobin measurement is the reference laboratory method for the quantitative determination of haemoglobin and is used for comparison and standardization of other methods. Some studies suggest that haemoglobin values measured in capillary samples are higher than those measured in venous samples, potentially leading to false-negative results (15).

Corrections of Hemoglobin in Relation to Body Muscle Mass in Asians

Primarily, Hemoglobin in the blood is required to carry oxygen from the respiratory organs to the rest of the body tissues. There Hb releases the oxygen to permit aerobic respiration of the tissues in the process called metabolism. The main biological function of hemoglobin is oxygen transport. Although, oxygen carrying capacity is proportional to the circulating hemoglobin concentration, an individual with chronic anemia develops a compensatory mechanism to improve oxygen unloading to tissue from hemoglobin during the resting state. This compensatory mechanism can maintain adequate tissue oxygen delivery down to a hemoglobin concentration of 70–80 g/L.

The associations between muscle mass and hemoglobin have been studied in different population groups. Among the elderly, this association has been studied in the light of decreasing muscle mass ("sarcopenia"), a normal stage of aging (19, 20). In endurance athletes, the effect of hemoglobin concentrations and muscle mass has been studied to look at the physiological parameters of oxygen delivery and ways to optimize it for better performance. There is no evidence to indicate that the hemoglobin cutoffs needs to be changed based on muscle mass, in light of these studies. At the same time, a reminder that hemoglobin cutoffs do have adjustments for other factors - race, age, gender, altitude - which may better reflect the differences in muscle mass, and we might consider that muscle mass adjustments are inherent in these factors. In an exercise state, however, any loss of hemoglobin or red blood cell mass can be detected as loss in work capacity, even within a hemoglobin range of 120-130 g/L (21).

There is inadequate scientific evidence available on the Hb cut off according to quantity of body muscle mass in the body. Even amongst athletes, hemoglobin concentration, packed cell volume and erythrocyte volume are directly correlated with the muscle mass. The aerobic requirements for muscular energy expenditure presumably provide the relevant feedback to the bone marrow for this purpose.

For a given body size, Indians have relatively lower muscle mass than Europeans, even at birth. Further, physical activity and energy expenditure of Indians has declined over time due to a sedentary lifestyle. This could partially explain the continuing high prevalence of mild anemia, even amongst high socio-economic strata. It also raises the interesting possibility that promotion of physical fitness and exercise in older children and adolescents could elevate hemoglobin levels in different settings (22).

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Tables

TABLE 1 HAEMOGLOBIN LEVELS TO DIAGNOSE ANAEMIA AT SEA LEVEL (G/L)

Population	Non-Anaemia*	Anaemia*		
		Mild	Moderate	Severe
Children 6-59 months of age	110 or higher	100-109	70-99	Lower than 70
Children 5-11 years of age	115 or higher	110-114	80-109	Lower than 80
Children 12-14 years of age	120 or higher	110-119	80-109	Lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	Lower than 80
Pregnant women	110 or higher	100-109	70-99	Lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	Lower than 80

** Haemoglobin in grams per litre*

TABLE 2 ALTITUDE ADJUSTMENTS TO MEASURED HAEMOGLOBIN CONCENTRATIONS (16)

Altitude (metres above sea level)	Measured haemoglobin adjustment (g/l)
<1000	0
1000	-2
1500	-5
2000	-8
2500	-13
3000	-19
3500	-27
4000	-35
4500	-45

TABLE 3 ADJUSTMENTS TO MEASURED HAEMOGLOBIN CONCENTRATIONS FOR SMOKERS (17,18)

Smoking status	Measured haemoglobin adjustment (g/l)
Non-smoker	0
Smoker (all)	-0.3
½ - 1 packet/day	-0.3
1-2 packets/day	-0.5
≥2 packets/day	-0.7