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ROLE OF HEMOGLOBIN AND ITS IMPACT ON HUMAN HEALTH-A NARRATIVE REVIEW

Narrative Review

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ABSTRACT

Background: Hemoglobin is a crucial protein in red blood cells, central to oxygen transport and delivery to tissues across the body. Variations in hemoglobin levels can significantly impact the function and health of various organs and systems. Both high and low hemoglobin levels are linked to a spectrum of physiological changes and are associated with various health outcomes. Understanding these effects is essential for advancing patient care and improving health outcomes through targeted management strategies.

Objective: This review aims to explore the impact of hemoglobin levels on the function of various human organs and body systems.

Findings: The review details how hemoglobin levels influence organ function through diverse physiological mechanisms. Abnormal hemoglobin levels are associated with cardiovascular diseases, respiratory and renal disorders, neurological impairments, gastrointestinal issues, metabolic conditions, and genetic diseases. By examining the intricate pathways through which hemoglobin affects organ health, this review supports the development of strategies for early detection, prevention, and management of hemoglobin-related health issues, thereby enhancing patient care.

Conclusion: This review emphasizes the importance of hemoglobin levels as a key determinant of organ function and health across different stages of life.

Keywords: Anemia, cardiovascular diseases, hemoglobin, human organ function, metabolic disorders, oxygen transport, red blood cells.

INTRODUCTION

Hemoglobin, a crucial protein found in red blood cells, plays an essential role in transporting oxygen from the lungs to various tissues and organs in the body (1). By ensuring efficient oxygen delivery, hemoglobin is instrumental in supporting cellular respiration, energy production, and blood pressure regulation. Additionally, hemoglobin contributes to thermal regulation by distributing heat throughout the body, which helps maintain a stable temperature necessary for optimal physiological functions (2). Another key function of hemoglobin includes transporting nitric oxide, a signaling molecule involved in vasodilation and blood flow regulation (3). Maintaining balanced hemoglobin levels is essential for human health, as both elevated and deficient levels are associated with a range of symptoms and health risks. Monitoring hemoglobin levels and managing underlying health conditions are critical for overall wellness. This review delves into the structure and function of hemoglobin and examines its significant effects on human health.

1.1 Structure and Functions of Hemoglobin

Hemoglobin is structured to optimize its primary function: oxygen transport. This globular protein consists of four subunits, each containing a heme group with an iron ion at its center. In adult humans, two alpha and two beta globin chains comprise the majority of hemoglobin, though variations exist across species and developmental stages. The heme group within each globin subunit enables hemoglobin to bind oxygen reversibly, allowing each molecule to carry up to four oxygen molecules—one per heme group. This reversible binding facilitates efficient oxygen loading in the lungs and release in tissues where oxygen levels are low (4-6). Hemoglobin's ability to adjust its oxygen affinity in response to changing physiological conditions is essential for tissue oxygenation. Factors such as pH, temperature, and the concentrations of carbon dioxide and other molecules influence hemoglobin's oxygen-binding affinity (7, 8). For instance, the Bohr effect describes how an increase in acidity (decreased pH) or carbon dioxide concentration reduces hemoglobin's affinity for oxygen, promoting oxygen release where it is most needed in tissues (9). Hemoglobin also serves as a blood buffer by binding hydrogen ions produced during bicarbonate formation, helping stabilize blood pH (10).

1.2 Allosteric Models of Hemoglobin

Allosteric models describe how oxygen binding to one hemoglobin subunit influences the oxygen affinity of other subunits. The Monod-Wyman-Changeux (MWC) model, or "concerted model," and the "sequential model" proposed by Perutz, are the most recognized allosteric models of hemoglobin behavior (11, 12). Both models provide insights into hemoglobin’s cooperative oxygen-binding mechanism. The MWC model posits that hemoglobin exists in two states: the tense (T) state and the relaxed (R) state, with the R state exhibiting a higher oxygen affinity. In the absence of oxygen, hemoglobin predominantly exists in the T state. However, when oxygen binds to one subunit, a conformational shift moves hemoglobin to the R state, increasing the affinity of the remaining subunits for oxygen and facilitating additional binding. Conversely, when oxygen is released, hemoglobin reverts to the T state, reducing oxygen affinity across subunits (12-14). The sequential model suggests that each hemoglobin subunit undergoes conformational changes upon oxygen binding, which incrementally affects neighboring subunits' affinity without strict T and R states. When oxygen binds to one subunit, it assumes an R-like conformation, stabilizing nearby subunits in a similar state and enhancing oxygen binding. When oxygen is released, the R-like conformation destabilizes, promoting oxygen release from adjacent subunits (12, 15, 16).

1.3 Factors Affecting Hemoglobin Levels

Several physiological and pathological factors influence hemoglobin levels, making it a valuable biomarker in medical practice. Age, gender, nutrition, chronic conditions, and genetics all play roles in determining hemoglobin concentration. Typically, hemoglobin levels increase from childhood to adulthood and are generally higher in adult males than females, mainly due to hormonal differences and menstrual cycles in females (17, 18). Adequate intake of iron, vitamin B12, folate, and copper is vital for hemoglobin synthesis, while deficiencies in these nutrients can result in anemia (19). Iron deficiency, one of the most common causes of low hemoglobin globally, can arise from insufficient dietary intake, blood loss, or impaired iron absorption due to medical conditions (20, 21). Chronic diseases such as chronic kidney disease, cancer, and inflammatory conditions can also affect hemoglobin levels by altering red blood cell production or lifespan (22, 23). Genetic factors, including thalassemia (24) and sickle cell disease (25), may disrupt hemoglobin structure or production, resulting in abnormal hemoglobin levels and anemia.

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1.4 Environmental factors

Environmental factors, such as altitude, can induce adaptive increases in hemoglobin to compensate for reduced oxygen availability. This adaptation enhances oxygen transport in tissues at higher altitudes (26). During pregnancy, hemoglobin levels typically decrease due to increased blood volume and iron requirements, which can lead to iron-deficiency anemia if nutritional intake is inadequate (27). Medications, including certain antiretroviral and chemotherapy drugs, can lower hemoglobin levels by impairing red blood cell production or promoting red blood cell breakdown. Treatments such as blood transfusions and erythropoiesis-stimulating agents may temporarily increase hemoglobin in patients with anemia (28). Acute blood loss from trauma, surgery, or gastrointestinal bleeding can cause sudden decreases in hemoglobin, potentially necessitating hemostatic interventions to restore blood volume and prevent anemia-related complications. In clinical settings, hemoglobin levels are routinely monitored to assess blood loss, guide treatment, and evaluate response to therapy in patients with anemia, chronic conditions, or cancer (29, 30).

1.5 Diseases Associated with Hemoglobin

Variations in hemoglobin levels significantly impact physiological functions and overall health, with abnormalities linked to various diseases and syndromes. Hemoglobin-related disorders include both acquired and hereditary conditions that alter hemoglobin's production, structure, or function.

1.5.1 Sickle Cell Disease

Sickle cell disease (SCD) is an inherited blood disorder characterized by the presence of hemoglobin S (HbS), an abnormal variant of hemoglobin. Under conditions such as low oxygen levels or dehydration, this genetic mutation causes red blood cells to stiffen and adopt a sickle or crescent shape. SCD is autosomal recessive, requiring an individual to inherit two faulty hemoglobin genes, one from each parent, to manifest symptoms. Carriers of a single mutated gene exhibit sickle cell trait and typically remain asymptomatic (31). In individuals with SCD, HbS molecules polymerize, causing red blood cells to become rigid and sticky, leading to clumping and blockages in blood vessels. This results in painful vaso-occlusive crises, where blood flow is obstructed, causing tissue damage and intense pain, often triggered by dehydration, infections, stress, or exposure to cold (32, 33). Sickle-shaped red blood cells have a shortened lifespan, leading to hemolytic anemia. Patients may experience complications such as acute chest syndrome, presenting with fever, cough, and chest pain, which can progress to respiratory failure and is a leading cause of mortality in SCD (34). Additionally, abnormal blood flow in SCD can impair oxygen delivery to the brain, increasing stroke risk, particularly in children. Patients with SCD are also at higher risk for bacterial infections due to impaired spleen function, and growth delays and cognitive challenges are common in affected children (35).

1.5.2 Thalassemia

Thalassemia is a group of genetic blood disorders caused by mutations affecting hemoglobin production. These mutations disrupt the synthesis of one or more globin chains in hemoglobin, resulting in reduced oxygen-carrying capacity (36). Alpha thalassemia results from mutations in one or more of the four alpha-globin genes. The severity of alpha thalassemia varies, ranging from silent carriers to hemoglobin H disease and the most severe form, hydrops fetalis, which is incompatible with life (37). Beta thalassemia arises from mutations in one or both beta-globin genes, with severity dependent on the mutation type. The most severe form, beta thalassemia major (Cooley's anemia), requires regular blood transfusions for survival. Beta thalassemia intermedia presents with less severe symptoms, though transfusions may still be needed, while beta thalassemia minor usually causes mild anemia and requires minimal or no treatment (38). Genetic counseling is recommended for individuals with thalassemia to assess reproductive options and transmission risk to future generations (39).

1.5.3 Iron Deficiency Anemia

Iron deficiency anemia (IDA) is the result of insufficient iron, a key component of hemoglobin. Without adequate iron, hemoglobin production decreases, reducing oxygen delivery to tissues and causing fatigue, weakness, and pallor. IDA is characterized by microcytic (small) and hypochromic (pale) red blood cells, a consequence of the bone marrow's inability to produce sufficient hemoglobin (40, 41). Inadequate dietary iron intake is a common cause of IDA, especially in populations with limited access to iron-rich foods (21). Chronic blood loss, including menstrual bleeding, gastrointestinal bleeding, or parasitic infections, can further reduce iron levels. Populations with increased iron needs, such as pregnant women, infants, and growing children, are particularly susceptible to IDA (42). Symptoms of IDA include fatigue and pallor due to reduced oxygen transport and impaired energy production, highlighting the importance of sufficient iron for maintaining hemoglobin levels (43).

1.5.4 Sideroblastic Anemia

Sideroblastic anemia is a disorder characterized by defective heme synthesis in the bone marrow, leading to iron accumulation in erythroid precursor cells' mitochondria. The hereditary form of sideroblastic anemia often manifests in childhood and may result from mutations in genes involved in heme synthesis, such as ALAS2, which encodes the enzyme aminolevulinate synthase 2. The acquired form, typically appearing in adulthood, can be induced by factors like vitamin B6 deficiency, alcoholism, myelodysplastic syndromes (MDS), exposure to toxins, or certain medications (44). Defective heme synthesis in sideroblastic anemia disrupts iron incorporation into heme, causing iron to accumulate within mitochondria. When stained with Prussian blue, bone marrow specimens from affected individuals display siderotic granules due to iron buildup, a hallmark finding of sideroblastic anemia (45).

1.5.5 Hemolytic Anemia

Hemolytic anemia is characterized by the premature destruction of red blood cells, which can occur within the liver, spleen, or bloodstream. Intrinsic hemolytic anemia results from red blood cell abnormalities, such as in thalassemia, SCD, and hereditary spherocytosis. Extrinsic hemolytic anemia is caused by external factors, including autoimmune reactions, infections, or exposure to drugs and toxins (46, 47). A peripheral blood smear in hemolytic anemia may reveal schistocytes (fragmented red blood cells) and an elevated reticulocyte count, reflecting increased red blood cell production. Laboratory findings include elevated lactate dehydrogenase (LDH) and indirect bilirubin levels, markers of increased hemolysis (48, 49).

1.5.6 Anemia of Chronic Disease

Anemia of chronic disease (ACD), or anemia of inflammation, commonly occurs with chronic inflammatory conditions such as cancer, autoimmune diseases, chronic infections, and inflammatory disorders. ACD involves impaired erythropoiesis and disruptions in iron metabolism due to prolonged inflammation. Inflammatory cytokines like TNF-alpha, IL-1, and IL-6 play key roles in ACD by reducing erythropoietin production and inhibiting its bone marrow response (50, 51). ACD is associated with various chronic conditions, including hepatitis, HIV, tuberculosis, and autoimmune diseases like rheumatoid arthritis. Certain cancers, especially those involving chronic inflammation, are also linked to ACD, as is chronic kidney disease (CKD), where inflammation and reduced erythropoietin production contribute to anemia (52, 53). Typical findings in ACD include low hemoglobin levels, normal or slightly reduced serum iron, low transferrin saturation, normal or elevated ferritin, and increased markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (54).

1.5.7 Polycythemia Vera

Polycythemia vera (PV) is a rare, chronic myeloproliferative disorder characterized by the excessive production of red blood cells (erythrocytosis), along with increased white blood cells and platelets. This overproduction results in increased blood volume and viscosity, which heightens the risk of thrombosis (blood clots) and hemorrhage (55). PV stems from a clonal expansion of hematopoietic stem cells, primarily driven by mutations in the JAK2 (Janus kinase 2) gene, particularly the JAK2 V617F mutation. This mutation activates the JAK-STAT signaling pathway, leading to uncontrolled proliferation and survival of blood cell progenitors (56, 57). Diagnostic findings for PV include elevated hemoglobin and hematocrit levels, increased white blood cell and platelet counts, and the presence of the JAK2 V617F mutation in bone marrow or peripheral blood. Bone marrow biopsy may reveal hypercellularity, reflecting an excess of erythroid, myeloid, and megakaryocytic cells (58).

CONCLUSION

This review underscores the intricate and dynamic role of hemoglobin in human health, extending beyond its traditional association with oxygen transport and cardiovascular function. Hemoglobin impacts a diverse range of physiological processes, including immune response, cognitive function, and endocrine balance, highlighting its relevance across multiple health domains. Genetic factors, environmental exposures, lifestyle choices, and concurrent health conditions further influence hemoglobin levels, adding layers of complexity to its clinical implications. These findings emphasize the need for a personalized approach in assessing, diagnosing, and managing hemoglobin-related conditions, recognizing the unique interplay between hemoglobin and overall health.

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REFERENCE

1. Michel J-B, Martin-Ventura JL. Red blood cells and hemoglobin in human atherosclerosis and related arterial diseases. International Journal of Molecular Sciences. 2020;21(18):6756.

2. Périard JD, Eijsvogels TM, Daanen HA. Exercise under heat stress: thermoregulation, hydration, performance implications, and mitigation strategies. Physiological reviews. 2021.

3. Shen X, Kaye AD, Cornett EM, Kevil CG. Nitric Oxide and Hemoglobin: Physiological Implications. Blood Substitutes and Oxygen Biotherapeutics: Springer; 2022. p. 93-7.

4. Ahmed MH, Ghatge MS, Safo MK. Hemoglobin: structure, function and allostery. Vertebrate and invertebrate respiratory proteins, lipoproteins and other body fluid proteins. 2020:345-82.

5. Faggiano S, Ronda L, Bruno S, Abbruzzetti S, Viappiani C, Bettati S, et al. From hemoglobin allostery to hemoglobin-based oxygen carriers. Molecular Aspects of Medicine. 2022;84:101050.

6. Olver CS. Erythrocyte structure and function. Schalm's veterinary hematology. 2022:158-65.

7. Wagner PD, editor Blood Gas Transport: Carriage of Oxygen and Carbon Dioxide in Blood. Seminars in Respiratory and Critical Care Medicine; 2023: Thieme Medical Publishers, Inc.

8. Webb KL, Dominelli PB, Baker SE, Klassen SA, Joyner MJ, Senefeld JW, et al. Influence of high hemoglobin-oxygen affinity on humans during hypoxia. Frontiers in physiology. 2022;12:763933.

9. Signore AV, Tift MS, Hoffmann FG, Schmitt TL, Moriyama H, Storz JF. Evolved increases in hemoglobin-oxygen affinity and the Bohr effect coincided with the aquatic specialization of penguins. Proceedings of the National Academy of Sciences. 2021;118(13):e2023936118.

10. Hopkins E, Sanvictores T, Sharma S. Physiology, acid base balance. StatPearls [Internet]: StatPearls Publishing; 2022.

11. Brunori M, Miele AE. Modulation of Allosteric Control and Evolution of Hemoglobin. Biomolecules. 2023;13(3):572.

12. Eaton WA. A retrospective on statistical mechanical models for hemoglobin allostery. The Journal of Chemical Physics. 2022;157(18).

13. Lavrinenko IA, Vashanov GA, Hernández Cáceres JL, Nechipurenko YD. Mathematical models describing oxygen binding by hemoglobin. Biophysical Reviews. 2023;15(5):1269-78.

14. Scrima R, Fugetto S, Capitanio N, Gatti DL. On the Origin of Hemoglobin Cooperativity under Non-equilibrium Conditions. Discoveries. 2022;10(2).

15. Karplus M, Case DA, Gelin B, Huynh BH, Lee AW-m, Szabo A. Structure and function of hemoglobin: the cooperative mechanism. Allosteric Enzymes: CRC Press; 2020. p. 27-59.

16. Pezzella M, El Hage K, Niesen MJ, Shin S, Willard AP, Meuwly M, et al. Water dynamics around proteins: T-and R-states of hemoglobin and melittin. The Journal of Physical Chemistry B. 2020;124(30):6540-54.

17. Achmad H, Arsyad A, Putra AP, Sukmana BI, Adiputro DL, Kasab J. Differences in VO 2 Max Based on Age, Gender, Hemoglobin Levels, and Leukocyte Counts in Hajj Prospective Pilgrims in Hulu Sungai Tengah Regency, South Kalimantan. Systematic Reviews in Pharmacy. 2020;11(4).

18. Neufingerl N, Eilander A. Nutrient intake and status in adults consuming plant-based diets compared to meat-eaters: A systematic review. Nutrients. 2021;14(1):29.

19. Bhadra P, Deb A. A review on nutritional anemia. Indian Journal of Natural Sciences. 2020;10(59):18466-74.

20. Abioye AI, Fawzi WW. Nutritional anemias. Present knowledge in nutrition: Elsevier; 2020. p. 503-21.

21. Bathla S, Arora S. Prevalence and approaches to manage iron deficiency anemia (IDA). Critical Reviews in Food Science and Nutrition. 2022;62(32):8815-28.

22. Salokhiddinovna XY. Anemia of Chronic Diseases. Research Journal of Trauma and Disability Studies. 2023;2(12):364-72.

23. Wiciński M, Liczner G, Cadelski K, Kołnierzak T, Nowaczewska M, Malinowski B. Anemia of chronic diseases: wider diagnostics—better treatment? Nutrients. 2020;12(6):1784.

24. Shafique F, Ali S, Almansouri T, Van Eeden F, Shafi N, Khalid M, et al. Thalassemia, a human blood disorder. Brazilian Journal of Biology. 2021;83.

25. Adekile A. The genetic and clinical significance of fetal hemoglobin expression in sickle cell disease. Medical Principles and Practice. 2021;30(3):201-11.

26. Mallet RT, Burtscher J, Pialoux V, Pasha Q, Ahmad Y, Millet GP, et al. Molecular mechanisms of high-altitude acclimatization. International journal of molecular sciences. 2023;24(2):1698.

27. Ogunbode O, Ogunbode O. Anaemia in pregnancy. Contemporary obstetrics and gynecology for developing countries. 2021:321-30.

28. Brittenham GM, Moir-Meyer G, Abuga KM, Datta-Mitra A, Cerami C, Green R, et al. Biology of anemia: a public health perspective. The Journal of Nutrition. 2023;153:S7-S28.

29. Barannik S, Korpusenko I, Trofimov M, Chukhriyenko A, Shevtsov V. PATHOPHYSIOLOGICAL CHANGES AND COMPENSATORY REACTIONS IN THE BODY OF THE VICTIM DUE TO MASSIVE BLEEDING AND BLOOD LOSS. Collection of scientific papers «SCIENTIA». 2023(January 20, 2023; Amsterdam, Netherlands):232-7.

30. Shaw JL, Nielson CM, Park JK, Marongiu A, Soff GA. The incidence of thrombocytopenia in adult patients receiving chemotherapy for solid tumors or hematologic malignancies. European journal of haematology. 2021;106(5):662-72.

31. Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a review. Jama. 2022;328(1):57-68.

32. Bender M, Carlberg K. Sickle cell disease. 2021.

33. Arishi WA, Alhadrami HA, Zourob M. Techniques for the detection of sickle cell disease: a review. Micromachines. 2021;12(5):519.

34. Tebbi CK. Sickle Cell Disease, a Review. Hemato. 2022;3(2):341-66.

35. Kirkham FJ, Lagunju IA. Epidemiology of stroke in sickle cell disease. Journal of Clinical Medicine. 2021;10(18):4232.

36. Aksu T, Unal S. Thalassemia. Trends in Pediatrics. 2021;2(1):1-7.

37. Tamary H, Dgany O. Alpha-thalassemia. 2020.

38. Origa R. Beta-thalassemia. 2021.

39. Ahmed S, Jafri H, Rashid Y, Ehsan Y, Bashir S, Ahmed M. Cascade screening for beta-thalassemia in Pakistan: development, feasibility and acceptability of a decision support intervention for relatives. European Journal of Human Genetics. 2022;30(1):73-80.

40. Lal A. Iron in health and disease: An update. The Indian Journal of Pediatrics. 2020;87(1):58-65.

41. Pasricha S-R, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. The Lancet. 2021;397(10270):233-48.

42. Lee NH. Iron deficiency anemia. Clinical Pediatric Hematology-Oncology. 2020;27(2):101-12.

43. Lee DT, Plesa ML. Anemia. Family Medicine: Principles and Practice: Springer; 2022. p. 1815-29.

44. Abu-Zeinah G, DeSancho MT. Understanding sideroblastic anemia: an overview of genetics, epidemiology, pathophysiology and current therapeutic options. Journal of blood medicine. 2020:305-18.

45. Rodriguez-Sevilla JJ, Calvo X, Arenillas L. Causes and Pathophysiology of Acquired Sideroblastic Anemia. Genes. 2022;13(9):1562.

46. Barcellini W, Zaninoni A, Giannotta JA, Fattizzo B. New insights in autoimmune hemolytic anemia: from pathogenesis to therapy. Journal of clinical medicine. 2020;9(12):3859.

47. Michalak SS, Olewicz-Gawlik A, Rupa-Matysek J, Wolny-Rokicka E, Nowakowska E, Gil L. Autoimmune hemolytic anemia: current knowledge and perspectives. Immunity & Ageing. 2020;17(1):1-16.

48. Scheckel CJ, Go RS. Autoimmune hemolytic anemia: Diagnosis and differential diagnosis. Hematology/Oncology Clinics. 2022;36(2):315-24.

49. Fermo E, Vercellati C, Bianchi P. Screening tools for hereditary hemolytic anemia: new concepts and strategies. Expert review of hematology. 2021;14(3):281-92.

50. Camaschella C, Weiss G. Anemia of chronic disease/anemia of inflammation. UpToDate Waltham, MA: UpToDate. 2020.

51. Akhtamovna ON. Anemia in Chronic Diseases. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1(10):722-9.

52. Kurkina N, Gorshenina E, Chegodaeva L, Polagimova A. Anemia of chronic diseases. Klinicheskaya onkogematologiya. 2021;14(3):347-54.

53. Ismaiel A, Srouji N. Al Anemia of Chronic Disease: Epidemiology and Pathophysiological Mechanisms—Literature Review. Glob J Med Ther. 2020;2:8-16.

54. Muxtorovna EM, Mamadiyarovich SA. New Opportunities in the Diagnosis of Anemia of Chronic Diseases. Genius Repository. 2023;27:24-30.

55. Grenier JM, El Nemer W, De Grandis M. Red Blood Cell Contribution to Thrombosis in Polycythemia Vera and Essential Thrombocythemia. International Journal of Molecular Sciences. 2024;25(3):1417.

56. Guglielmelli P, Vannucchi AM. Current management strategies for polycythemia vera and essential thrombocythemia. Blood Reviews. 2020;42:100714.

57. Regimbeau M, Mary R, Hermetet F, Girodon F. Genetic background of polycythemia vera. Genes. 2022;13(4):637.

58. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. American journal of hematology. 2023;98(9):1465-87.