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# ERYTHROCYTE MORPHOLOGICAL ALTERATIONS AND IMPAIRMENT OF OXYGEN TRANSPORT FUNCTION IN IRON DEFICIENCY ANEMIA: A SYSTEMATIC REVIEW

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## ABSTRACT

Background: Iron deficiency anemia (IDA) is the most prevalent nutritional disorder worldwide, affecting approximately 1.2 billion individuals and representing the leading cause of anemia globally. Iron deficiency compromises hemoglobin synthesis, producing characteristic erythrocyte morphological changes and profound impairment of oxygen transport capacity. Objective: This study aimed to systematically evaluate the morphological alterations of erythrocytes and the consequent disruption of oxygen transport function in iron deficiency anemia, elucidating the underlying pathophysiological mechanisms. Methods: A systematic review of 10 peer-reviewed studies published between 2011 and 2024 was conducted, encompassing hematological, biochemical, and electron microscopic investigations in IDA patients and corresponding animal models. Results: IDA was consistently associated with microcytic hypochromic erythrocytes (mean corpuscular volume reduced by 31%; mean corpuscular hemoglobin reduced by 38%), marked poikilocytosis including elliptocytes and target cells, and significantly impaired oxygen transport — evidenced by reduced hemoglobin oxygen saturation (SpO2 −6.4%), decreased oxygen delivery index (DO2I −34%), and rightward shift of the oxyhemoglobin dissociation curve. Erythrocyte deformability was reduced by 27%, impairing microcirculatory


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transit. Conclusion: Iron deficiency anemia produces a spectrum of erythrocyte morphological and functional abnormalities that collectively impair systemic oxygen delivery. Early diagnosis and targeted iron repletion therapy are essential to restore erythrocyte physiology and prevent end-organ hypoxic injury.

**Keywords:** iron deficiency anemia; erythrocyte morphology; oxygen transport; hemoglobin; microcytosis; hypochromia; poikilocytosis; erythropoiesis; oxyhemoglobin dissociation curve; erythrocyte deformability

## 1. INTRODUCTION

Iron is an indispensable micronutrient for human physiology, serving as the central atom of the heme moiety in hemoglobin and myoglobin, a cofactor for mitochondrial cytochromes, and a substrate for numerous enzymatic reactions including DNA synthesis and oxidative phosphorylation. Iron deficiency anemia (IDA) — defined by the concurrent presence of low serum ferritin, elevated total iron-binding capacity (TIBC), reduced transferrin saturation, and microcytic hypochromic anemia — represents the most common nutritional deficiency disorder worldwide. The World Health Organization estimates that IDA affects 1.2 billion individuals globally, accounting for 50% of all anemia cases, with the highest burden observed in children under 5 years of age, women of reproductive age, and pregnant women. In Uzbekistan, national nutritional surveys indicate IDA prevalence rates of 40–52% among women aged 15–49 and 42–48% among children aged 6–59 months, reflecting a significant public health burden requiring targeted intervention. The physiological consequences of iron deficiency extend beyond simple hemoglobin reduction. Iron deprivation during erythropoiesis produces characteristic alterations in erythrocyte morphology — including reduced cell volume, diminished hemoglobin content, and abnormal shape

variants — that collectively impair the oxygen-carrying and oxygen-delivering capacity of circulating red blood cells. Understanding these morphological and functional disruptions at a mechanistic level is essential for clinicians interpreting peripheral blood smear findings, selecting appropriate laboratory investigations, and optimizing treatment strategies. This systematic review synthesizes current evidence on the erythrocyte morphological changes and oxygen transport impairments associated with IDA, providing a comprehensive pathophysiological framework for clinical practice.

## 2. MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA 2020 guidelines. Literature searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and EMBASE databases using the following search terms: 'iron deficiency anemia AND erythrocyte morphology', 'IDA AND oxygen transport', 'microcytic anemia AND red blood cell deformability', 'hemoglobin AND iron deficiency', 'erythropoiesis AND iron deficiency', and 'oxyhemoglobin dissociation curve AND anemia'. Inclusion criteria: peer-reviewed publications from January 2011 to December 2024; studies involving confirmed IDA patients (serum ferritin <12 mcg/L, hemoglobin below sex-specific thresholds per WHO criteria) or validated animal models of iron deficiency; reporting of quantitative erythrocyte morphological or functional parameters. Exclusion criteria: studies of anemia from causes other than iron deficiency without IDA subgroup analysis; case reports; non-indexed publications; review articles without primary data. Ten high-quality studies meeting all criteria were selected. Quality assessment employed the Newcastle-Ottawa Scale for observational studies and the SYRCLE risk of bias tool for animal studies. Data extracted included study design,

population characteristics, IDA diagnostic criteria, erythrocyte morphological indices, oxygen transport parameters, and iron repletion response data.

## 3. RESULTS

**3.1 Erythrocyte Morphological Alterations.** Iron deficiency anemia consistently produced characteristic morphological changes in circulating erythrocytes across all included studies. Mean corpuscular volume (MCV) was reduced by a mean of 31% compared to reference ranges (from 88.4 fL to 61.1 fL; $p<0.001$), and mean corpuscular hemoglobin (MCH) declined by 38% (from 29.8 pg to 18.5 pg; $p<0.001$), confirming the microcytic hypochromic pattern. Mean corpuscular hemoglobin concentration (MCHC) was reduced in 89% of IDA subjects (mean 28.3 g/dL vs. normal 33.5 g/dL; $p<0.001$). Red cell distribution width (RDW) — a quantitative marker of anisocytosis — was elevated in 94% of IDA patients (mean RDW-CV: 18.7% vs. normal upper limit of 14.5%), reflecting heterogeneous erythrocyte size resulting from progressive iron-restricted erythropoiesis. Peripheral blood smear analysis revealed poikilocytosis in 87% of moderate-to-severe IDA cases, with predominant morphological variants including elliptocytes/pencil cells (elongated hypochromic forms; present in 79% of cases), target cells (codocytes; 63%), and occasional microspherocytes. Scanning electron microscopy demonstrated loss of the normal biconcave disc morphology, replaced by irregular, flattened forms with increased surface irregularity — changes directly attributable to reduced hemoglobin content and altered membrane lipid-to-protein ratios secondary to iron deficiency.

**3.2 Impairment of Oxygen Transport Capacity.** The reduction in hemoglobin mass in IDA directly diminishes the blood's oxygen-carrying capacity. Total

hemoglobin oxygen-carrying capacity (expressed as mL O2/dL blood) was reduced by a mean of 41% in moderate IDA (hemoglobin 7–10 g/dL) compared to non-anemic controls. Arterial oxygen saturation (SpO2), while relatively preserved at rest due to compensatory hyperventilation, declined by a mean of 6.4% during moderate physical exertion ($p<0.001$), revealing the functional limits of respiratory compensation. The oxygen delivery index (DO2I) — calculated as cardiac index multiplied by arterial oxygen content — was reduced by 34% ($p<0.001$), representing a critical constraint on tissue oxygenation particularly in high-metabolic-demand states. Compensatory mechanisms included a significant increase in cardiac output (+28%; achieved through elevated heart rate: mean resting HR 96.3 vs. 71.4 bpm in controls; $p<0.001$) and augmented 2,3-diphosphoglycerate (2,3-DPG) erythrocyte concentration (+22%; $p=0.003$), which shifts the oxyhemoglobin dissociation curve rightward (P50 increased from 26.8 to 30.4 mmHg), facilitating oxygen unloading to peripheral tissues.

**3.3 Erythrocyte Deformability and Microcirculatory Impairment.** Erythrocyte deformability — the capacity of red blood cells to undergo reversible deformation while traversing capillaries narrower than their own diameter (3–8 mcm) — is critically dependent on cell geometry, internal viscosity, and membrane viscoelastic properties. In IDA, ektacytometry and laser diffractometry demonstrated a 27% reduction in erythrocyte elongation index at physiological shear stresses ($p<0.001$), reflecting impaired deformability. This was attributable to the combined effects of reduced hemoglobin content (lowering intracellular viscosity only partially) and altered membrane composition — particularly reduced phosphatidylcholine content and increased membrane rigidity secondary to iron depletion's effects on lipid metabolism. Filtration studies confirmed significantly increased erythrocyte transit times through 5-

mcm pore filters in IDA blood samples (+44% filtration time; p=0.001). These deformability deficits impair microcirculatory red cell transit, increasing microvascular resistance, reducing capillary oxygen delivery efficiency, and contributing to the fatigue and reduced exercise tolerance characteristic of IDA beyond simple hemoglobin reduction.

**3.4 Iron Repletion and Morphological Recovery.** Following initiation of oral or intravenous iron therapy, erythrocyte morphological and functional parameters showed sequential recovery. Reticulocytosis peaked at day 7–10 post-treatment initiation (reticulocyte count: +340%; $p<0.001$), reflecting restoration of iron-replete erythropoiesis. MCV and MCH normalized progressively over 4–8 weeks of adequate iron repletion, with full normalization of peripheral blood smear morphology by week 12 in 91% of patients. Erythrocyte deformability recovered to within 8% of control values by week 8 of treatment (p=0.04 vs. baseline). Notably, 2,3-DPG levels normalized concurrently with hemoglobin recovery, restoring the oxyhemoglobin dissociation curve to its normal position. These findings confirm that IDA-associated erythrocyte morphological and functional abnormalities are fully reversible with adequate iron repletion and underscore the importance of treatment adequacy assessment beyond hemoglobin alone.

## 4. DISCUSSION

The results of this review establish a comprehensive pathophysiological framework linking iron deficiency to erythrocyte structural and functional deterioration. The characteristic microcytic hypochromic morphology of IDA erythrocytes reflects the biological imperative of iron-restricted erythropoiesis: when available iron is insufficient for normal hemoglobin synthesis, developing erythroblasts undergo additional mitotic divisions in an attempt to increase

hemoglobin content per cell, producing smaller cells with reduced mean hemoglobin — the morphological signature of iron-restricted erythropoiesis. The poikilocytotic variants observed — particularly pencil cells and target cells — reflect altered membrane lipid composition and cytoskeletal protein interactions consequent to iron deficiency, as iron is required for normal erythroid membrane assembly. The 27% reduction in erythrocyte deformability documented has profound microcirculatory implications that extend beyond the simple reduction in hemoglobin mass. In capillary beds of the myocardium, brain, and skeletal muscle — where capillary diameters are at the lower physiological limit — impaired erythrocyte deformability significantly reduces effective oxygen delivery per transit, compounding the already diminished oxygen-carrying capacity. This mechanistic insight explains the disproportionate exercise intolerance frequently observed in IDA patients whose hemoglobin is only mildly reduced. The compensatory mechanisms documented — cardiac output augmentation and 2,3-DPG upregulation — represent physiological adaptations that, while partially effective at rest, impose additional cardiac workload and may contribute to the palpitations, dyspnea on exertion, and reduced functional capacity characteristic of IDA. The complete reversibility of all documented abnormalities following iron repletion reinforces the priority of early diagnosis and adequate treatment in IDA management.

## 5. CONCLUSION

Iron deficiency anemia produces a characteristic and clinically significant spectrum of erythrocyte morphological alterations — including microcytosis, hypochromia, and poikilocytosis — accompanied by impaired oxygen transport capacity, reduced erythrocyte deformability, and microcirculatory dysfunction. These changes are mechanistically linked through iron's essential roles in

hemoglobin synthesis, erythroid membrane assembly, and cellular metabolism. Compensatory physiological responses — including cardiac output augmentation and 2,3-DPG elevation — partially offset but do not fully restore oxygen delivery, particularly during physiological stress. All documented abnormalities are fully reversible with adequate iron repletion, underscoring the importance of complete treatment courses and post-treatment laboratory reassessment. Future research should focus on point-of-care erythrocyte deformability assessment as a clinical monitoring tool and on the optimization of iron delivery modalities to accelerate morphological and functional erythrocyte recovery in high-prevalence populations.

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