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Review Article

Anemia: Etiology, Epidemiology, Pathophysiology, and Prevention Strategies with Special Reference to India

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ABSTRACT

Anemia, marked by reduced hemoglobin levels or red blood cell mass, poses a critical global health challenge—particularly across low- and middle-income countries. This project offers a comprehensive examination of anemia's diverse etiology, epidemiology, clinical presentations, and preventive frameworks, with a particular emphasis on its high prevalence in India. Despite sustained public health efforts, anemia disproportionately affects children, adolescent girls, and pregnant women, largely due to nutritional deficiencies, infectious diseases, suboptimal diets, socioeconomic disadvantages, and limited access to care. The study explores key anemia types—iron-deficiency, megaloblastic, hemolytic, aplastic, sickle cell anemia, and thalassemia—detailing their pathophysiology, morphological changes, clinical signs, and diagnostic protocols. It highlights the essential role of iron, folate, and vitamin B_{12} in hematopoiesis and how their deficiencies amplify disease burden. Drawing on WHO and NFHS data, the project reveals significant regional disparities, especially in states like Bihar, where gender-based inequities and cultural factors intensify vulnerability. Beyond clinical concerns, the study addresses anemia's broader socioeconomic impacts—linking untreated cases to impaired child development, lowered productivity, higher maternal mortality, and losses to national GDP.

Keywords: *Anemia, Iron-deficiency anemia (IDA), Nutritional deficiencies, Hemoglobinopathies, Maternal and child health, Micronutrient supplementation, WHO.*

Introduction

Anaemia is a condition in which the number of red blood cells (RBCs), and consequently their oxygen-carrying capacity, is insufficient to meet the body's physiological needs. The function of the RBCs is to deliver oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. Anemia results from one or more of the following process: defective red cell production, increased red cell destruction or blood loss. Iron is necessary for synthesis of haemoglobin. Iron deficiency is thought to be the most common cause of anemia globally, but other nutritional deficiencies (including folate, vitamin B12 and vitamin A), acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect Hb synthesis, red blood cell production or red blood cell survival can all cause anaemia. Iron deficiency anaemia results in impaired cognitive and motor development in children and decreased work capacity in adults. The effects are most severe in infancy and early childhood. In pregnancy iron deficiency anaemia can lead to perinatal loss, prematurity and low birth weight (LBW) babies. Iron deficiency anaemia also adversely affects the body's immune response [1].

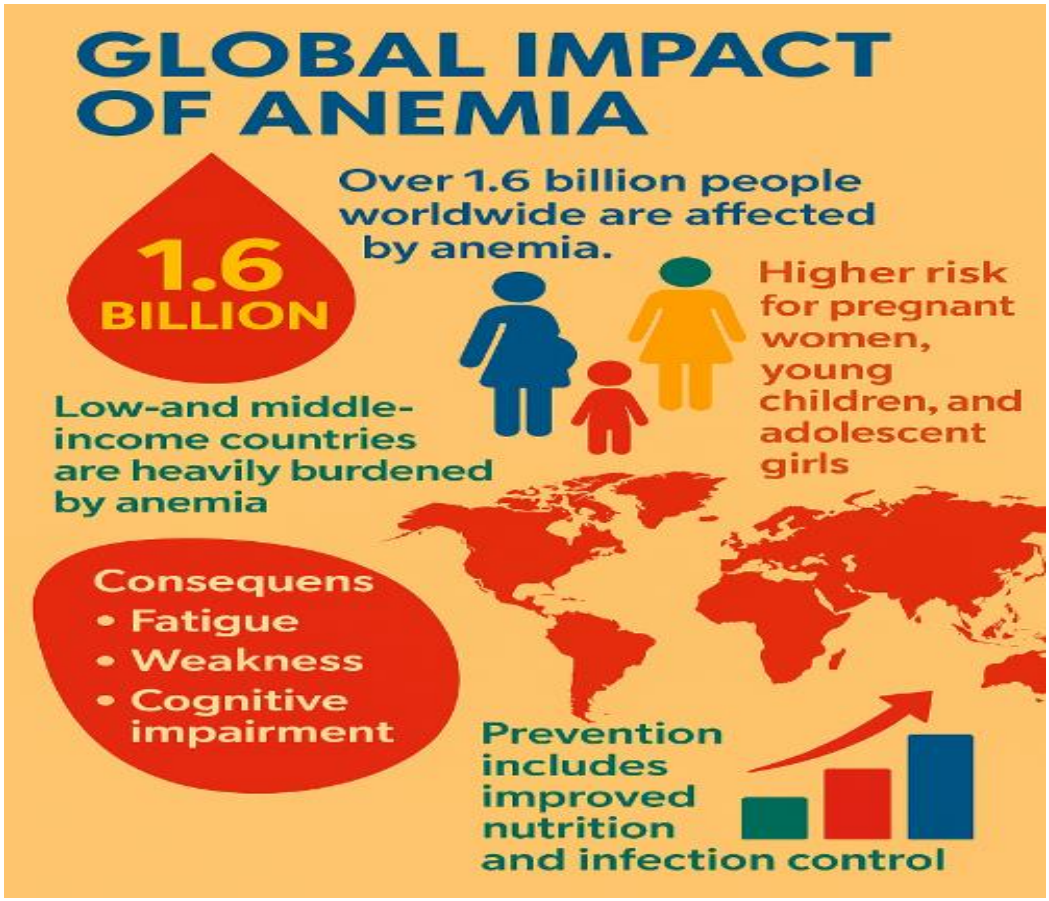

Figure 1: Global impact of anemia.

Global Burden of Anemia

Health is a fundamental human right that is recognised by international law. Unfortunately, treatable and preventable diseases persist. One of many such diseases is anaemia, which WHO estimates affects 1·8 billion people worldwide. 40% of all children aged 6–59 months and 30% of women aged 15–49 years (increasing to 37% of pregnant women) have anaemia, with the highest prevalence in sub-Saharan Africa and Asia. Understanding the extent and distribution of anaemia morbidity and mortality, and contextualising it within human disease more broadly, is crucial for addressing health inequality and improving health outcomes. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) aims to comprehensively catalogue and quantify the impact of different diseases, risk factors and injuries so that their effect on health can be understood and addressed. To achieve this aim, relative harm from different diseases must first be converted into a common unit for comparison. Years lived with disability (YLDs) is used to quantify the impairment associated with living with a condition, and years of life lost (YLLs) is used to quantify the effect of early death [2]. These measures can be combined to estimate the disability-adjusted life-years (DALYs) attributable to a disease or condition. YLDs is calculated by combining the prevalence and duration of an illness with its severity, which is quantified by its disability weight (a disease-specific estimate derived from large population surveys of perceived disease severity). In The Lancet Haematology, the GBD 2021 Anaemia Collaborators present estimates of the global burden of anaemia.4 The authors report that the total number of people with anaemia increased from 1·50 billion (95% uncertainty interval 1·48–1·52) in 1990 to 1·92 billion (1·89–1·95) in 2021, although the prevalence of anaemia decreased slightly, from 28·2% (27·8–28·5) to 24·3% (23·9–24·7), over this period. The prevalence of anaemia in 2021 remained highest in western sub-Saharan Africa (47·4%), south Asia (43·0%), and central sub-Saharan Africa (35·7). The total number of YLDs due to anaemia increased from 46·6 million (31·6–65·7) in 1990 to 52·0 million (35·1–75·1) in 2021, when anaemia resulted in 659·2 (444·9–952·3) YLDs per 100000 population. Overall, anaemia is responsible for 5·7% of all YLDs globally, making it the third leading cause of disability worldwide. Iron deficiency is the leading cause of anaemia YLDs in most places worldwide, especially in women. It is concerning that the decrease in anaemia prevalence

over time has been proportionally greater in men than in women. The study provides highly valuable, country-specific estimates of anaemia prevalence and anaemia YLDs and estimates of cause-specific anaemia prevalence. The analyses show that moderate and severe anaemia account for the highest disease burden, despite being less prevalent than mild anaemia. This finding is attributable to severity-based disability weights for anaemia (mild anaemia 0·004, moderate anaemia 0·052, and severe anaemia 0·149) and is corroborated by previous analyses indicating that iron interventions have greater benefit– risk ratio and cost-effectiveness in settings where moderate and severe anaemia is more prevalent.5 This insight offers a new approach to monitoring the decrease of the anaemia burden: perhaps more YLDs could be averted if addressing moderate and severe anaemia was prioritised. However, estimates of YLDs due to anaemia do not encompass the potential downstream effects of the condition. For example, in pregnancy, mild anaemia can affect multiple birth outcomes6 and result in low birthweight, which itself is associated with an increased risk of diabetes and cardiovascular disorders in later life. In children, anaemia can result in impaired developmental outcomes, although these do not appear to be reversible by iron interventions in infancy.7 Moreover, anaemia is consistently identified as a risk factor for death from various medical conditions.8 These secondary effects of anaemia suggest that the GBD approach could underestimate the true effects of anaemia. It is important to note that longitudinal estimates of anaemia prevalence and disease burden are not based on anaemia incidence itself but are derived from models incorporating multiple covariates. These measures include the 50th centile of haemoglobin concentration; Socio-demographic Index; fertility rates; prevalence of HIV, child underweight, child wasting, haemoglobin C and S trait, and impaired kidney function; malaria incidence; health-care access and quality; gross domestic product per capita; and use of modern contraceptives. Some of these covariates could directly influence haemoglobin concentrations (eg, malaria and haemoglobin variants), whereas others could influence anaemia indirectly (eg, contraceptives), and still others reflect upstream conditions [3]. Acknowledging that apparent changes in anaemia prevalence could reflect changes in the epidemiology of covariates is therefore important. Addressing anaemia is a global health priority, with both WHO9 and the UN Sustainable Development Goals10 setting ambitious anaemia reduction targets. The GBD 2021 anaemia estimates both provide a timely reminder that monitoring the prevalence of anaemia alone is insufficient to monitor the effects of this condition and help to identify potential unmet needs for prioritization.

Etiology of Anemia

Understanding the different types of anaemia requires an examination of their causes, particularly in relation to blood cell morphology. Variations in the size, shape, and color of red blood cells (RBCs) can indicate specific underlying conditions, thereby aiding in accurate diagnosis and appropriate treatment. Morphological classifications are essential in distinguishing between different types of anaemia, such as microcytic, normocytic, and macrocytic anaemia. Each of these types is associated with distinct causes: microcytic anaemia is typically due to iron deficiency, normocytic anaemia may result from chronic disease or acute blood loss, and macrocytic anaemia is commonly linked to vitamin B12 or folic acid deficiencies [4].

Table 1: Causes of anemia based on blood cell morphology

Types of Anemia	Reason
Aplastic Anemia	Damage to the marrow bones
Microcytic anemia	Lack of substance iron
Normocytic Anemia	Anemia caused by chronic disease, disorder production cell blood red with marrow bones, as well as failure kidneys function, bleeding.
Hemolytic Anemia	Damage to cells' blood red that has not yet reached the stage of maturity
Macrocytic anemia (megaloblastic & pernicious)	Vitamin B12 deficiency, lack of sour folate, and disturbance in protein synthesis, autoimmune disease.
Anemic Hemoglobinopathies	Disturbance genetic causes cell blood to red own form like sickle and thalassemia

Increased Physiological Requirements

Iron is critical to a variety of core biological functions including energy metabolism, nucleotide synthesis, neurogenesis, and oxygen carriage or storage. Because the only physiological source is dietary intake, iron is an essential nutrient. The demand for iron is the highest from the erythroid compartment for incorporation into hemoglobin (Hb) molecules in red blood cells (RBCs). Iron is released from RBCs as they senesce, then scavenged by macrophages and promptly made available for distribution to the plasma. Reduced iron availability for erythropoiesis can occur as a result of absolute ID (insufficient iron stores) or functional ID (inadequate iron mobilization despite adequate iron stores). Absolute ID is especially prevalent in children under 5 y of age and in women of childbearing age, particularly during pregnancy. Functional ID is prevalent in populations in areas where infection is common, in complicated medical and surgical disorders, and in patients receiving erythropoiesis stimulating agents. When iron availability for erythropoiesis is limited, whether from absolute or functional ID, reduced Hb production can lead to poor oxygen transport, and eventually, anemia. Absolute ID can arise from both increased physiological requirements and pathological losses, from insufficient dietary iron intake; insufficient iron absorption; or iron demand exceeding iron supply as a result of growth, pregnancy, hemolysis, bleeding, or treatment with erythropoiesis stimulating agents. Systemic iron regulation converges on a liver-derived regulatory hormone, hepcidin, encoded by the gene hepcidin antimicrobial peptide (HAMP). Hepcidin prevents iron entering the circulation by occluding the cellular iron export channel on the surface of duodenal enterocytes and macrophages while simultaneously initiating FPN ubiquitination and degradation. Liver iron-sensing mechanisms respond to increased iron stores or circulating iron to induce HAMP expression, whereas ID, erythropoiesis, and hypoxia downregulate expression of HAMP. Systemic inflammation can also induce hepcidin, despite the presence of iron deficits or absolute ID. Even in the presence of replete-iron stores, inflammatory upregulation of hepcidin can limit iron supply and result in functional ID and anemia [5].

Pathophysiology of Anemia

The pathophysiology of anemia varies greatly depending on the primary cause. For instance, in acute hemorrhagic anemia, it is the restoration of blood volume with intracellular and extracellular fluid that dilutes the remaining red blood cells (RBCs), which results in anemia. A proportionate reduction in both plasma and red cells results in falsely normal hemoglobin and hematocrit.

RBC are produced in the bone marrow and released into circulation. Approximately 1% of RBC are removed from circulation per day. Imbalance in production to removal or destruction of RBC leads to anemia.

The main mechanisms involved in anemia are listed below:

1. Increased RBC destruction
Blood loss
Acute- hemorrhage, surgery, trauma, menorrhagia
Chronic- heavy menstrual bleeding, chronic gastrointestinal blood losses (in the setting of hookworm infestation, ulcers, etc.), urinary losses (BPH, renal carcinoma, schistosomiasis)
Hemolytic anemia
Acquired- immune-mediated, infection, microangiopathic, blood transfusion-related, and secondary to hypersplenism
Hereditary- enzymopathies, disorders of hemoglobin (sickle cell), defects in red blood cell metabolism (G6PD deficiency, pyruvate kinase deficiency), defects in red blood cell membrane production (hereditary spherocytosis and elliptocytosis)

2. Deficient/defective erythropoiesis
Microcytic
Normocytic, normochromic
Macrocytic

Impaired Erythropoiesis

Erythropoiesis and the erythroblastic island

Erythropoiesis occurs in specialized niches within the bone marrow and the spleen consisting of a central nursing macrophage surrounded by erythroid cells in different stages of differentiation. Although the first erythroblastic island was observed by Bessis et al. through electron micrographs, long term liquid cultures of bone marrow cells have also been used to generate erythroblastic islands in vitro. Erythroblastic islands have also been isolated and cultured from spleens of phlebotomized mice, where the central stromal macrophage extended cytoplasmic processes to surrounding erythroblasts with the latter also exhibiting differentiation. Moreover, cell to cell adhesion has been shown to be a key factor regulating erythroid differentiation in an erythroblastic island. This is not only mediated by the erythoblast macrophage protein as demonstrated extensively using knock-out mice of this protein that are embryonic lethal, but also by the intracellular adhesion molecule-4 (Icam-4) such that mice lacking Icam-4 show significantly reduced erythroblastic islands [6]. Furthermore, blocking the interaction between Icam-4 on erythroid cells and alpha V integrin on

macrophages results in a marked reduction of erythroblastic islands. Interaction between VCAM-1 and Beta-1 integrin has also been implicated in erythroid macrophage contact within the erythroblastic island. Erythropoiesis within erythroblastic islands consists of multiple developmental stages. Erythroid progenitor proliferation begins as multipotent HSCs hematopoietic stem cells (HSC) proliferate and differentiate into burst forming unit-erythroid (BFU-E) stage which in turn gives rise to colony forming unit-erythroid (CFU-E). Terminal erythroid differentiation begins at the pro-erythroblast stage. This stage undergoes three consecutive mitosis to generate basophilic erythroblast followed by polychromatic erythroblast and then orthochromatic erythroblasts. The orthochromatic cells expel their nuclei to generate reticulocytes which undergo further changes to give rise to erythrocytes or RBCs. The different stages of terminal erythroid differentiation have been elucidated both by sequencing of RNA and by morphology [7].

Hepcidin and iron homeostasis

Hepcidin (HAMP) is considered a key regulatory molecule of systemic iron homeostasis, produced primarily by hepatocytes. HAMP acts as a negative regulator of iron availability by preventing export of iron from duodenal enterocytes, hepatocytes, macrophages and placental trophoblasts. High levels of HAMP trigger hypoferremia, as evidenced by studies where a single dose of 50 ug of HAMP in mice caused a rapid drop in serum iron in 1 hour. HAMP carries out this negative regulation of iron availability by directly binding to and degrading the iron exporter FPN [8]. In a feedback loop, HAMP in itself is also regulated by the element it controls: iron. This happens such that when iron levels are plentiful, HAMP expression is upregulated. Conversely, under conditions of iron deficiency, HAMP expression is downregulated, releasing iron into circulation thereby increasing TF saturation and plasma iron levels. One pathway controlling HAMP expression involves iron availability and the presence of holo-TF. This is mediated by the membrane protein HFE. Under conditions of high serum iron levels and TF-saturation or increased concentrations of holo-transferrin, the membrane protein HFE, generally sequestered away by binding to TFR1 is displaced to transferrin receptor 2 (TFR2), thereby forming an Fe-TF, HFE, TFR2 complex. This complex has been implicated in upregulating transcription of HAMP. The key pathway in inducing expression of HAMP involves BMP6, binding to the BMP receptor I and II complex including the BMP coreceptor Hemojuvelin (HJV), which confers sensitivity of binding. Activation of the BMP receptor leads to phosphorylation of SMAD1/5/8 in the cytosol and the latter then goes on to interact and form a complex with SMAD 4 which translocates to the nucleus and induces expression of HAMP. A serine protease Matriptase -2 encoded by the TMPRSS6 gene is capable of cleaving the BMP coreceptor HJV. Thus, it negatively regulates expression of HAMP such that TMPRSS6−/− mice have severe iron deficiency anemia.

Stress and ineffective erythropoiesis

Erythropoiesis is driven by the kidney hormone erythropoietin (EPO) (Figure 1). EPO binding to the EPO-receptor triggers activation of JAK2 and phosphorylated JAK2 can bind to STAT5 wherein the JAK2-STAT5 complex translocates to the nucleus and induces expression of target genes30 including but not limited to IREB2 (Iron responsive element binding protein 2) and anti-apoptotic factors such as BCL-XL31. Under conditions of acute blood loss or demands for increased oxygenation, the existing cellular hypoxia controls EPO expression through Hypoxia Inducible factor alpha 2 (HIF2 alpha) [9]. Upregulated EPO expression elicits an increased erythropoietic response, referred to as stress erythropoiesis. Stress erythropoiesis is characterized by an imbalance of erythroid proliferation and differentiation axis, resulting in an expansion of the erythroid progenitor pool to meet the demands of increased RBC generation and oxygenation. Erythropoiesis extends to extramedullary sites such as the liver and the spleen, and indeed splenomegaly is another hallmark of stress erythropoiesis. Under these conditions increased iron absorption is facilitated by the erythroid factor erythroferrone (ERFE) produced by erythroid progenitors which acts on the liver by an as yet unknown mechanism to suppress HAMP expression. This, with a concurrent upregulation of EPO, works to increase generation of RBC, iron availability and oxygenation of tissues under conditions of stress erythropoiesis. A chronic state of stress erythropoiesis seen in certain disorders is referred to as ineffective erythropoiesis. Under ineffective erythropoiesis, the imbalance of erythroid proliferation and differentiation is characterized by an increase in erythroblast proliferation that fails to differentiate and give rise to enucleate RBCs thereby resulting in anemia. The disease model of β-thalassemia has been used to study and characterize ineffective erythropoiesis. In face of a lack of decreased generation of beta globin chains, there is an accumulation of alpha chains that get deposited on erythroid membranes, generating hemichromes, causing substantial oxidative stress and cell death. As result of this, despite an expansion of the erythroid progenitor pool, a continuous state of chronic stress erythropoiesis ensues and the expanded pool of erythroid precursors are unable to generate RBCs. The

resulting anemia is also accompanied by a decrease in expression of HAMP, thereby increasing iron availability. Indeed, it has been shown that Erfe expression is upregulated in mouse model of beta thalassemia intermedia (Hbb th3/+). Thus, despite the inability to generate RBCs due to apoptosis of erythroid precursors, the ineffective erythropoiesis in beta thalassemia is characterized by increased serum EPO levels and concurrent fall in Hamp levels, leading to increased iron absorption and iron overload. The pathophysiology of ineffective erythropoiesis has been attributed in part to macrophages, which are a key component of erythroblastic islands within the bone marrow and the spleen. Depletion of macrophages by clodronate encapsulated liposomes or by using CD169 DTR mice substantially ameliorated anemia and splenomegaly seen in a mouse model of beta thalassemia intermedia. The various proteins and pathways implicated in maintaining contact between the central nursing macrophage and surrounding erythroblasts, including FAK (focal adhesion kinase) signaling downstream of alpha4beta1 integrin potentially contributes to macrophage mediated pathophysiology seen in the ineffective erythropoiesis of beta thalassemia. The underlying mechanism of this remains unknown. There are also other factors that have also been implicated in anemia associated with ineffective erythropoiesis seen in beta thalassemia, primarily associated with the imbalance of alpha-beta chains. One such factor is HSP 70 (heat shock protein 70) which translocates to the nucleus and protects the erythroid transcription factor GATA1 from cleavage by caspase 3. In in-vitro studies of human BM erythroblasts from beta thalassemic patients it has been shown that HSP 70 is sequestered by alpha chains as a result of which GATA1 is cleaved and erythroid maturation is impaired. Another factor is GDF11, a member of the TGF beta super family that has been shown to be elevated in both beta thalassemia and another disorder exhibiting some hallmarks of ineffective erythropoiesis, MDS (Myelodysplastic syndrome). There is also work to indicate that blocking GDF11 using trap ligands can reduce precipitation of alpha globin chains on erythroid membranes and subsequent oxidative stress, although the complete mechanism has not been completely elucidated. In the absence of transfusion therapy, ineffective erythropoiesis in beta thalassemia patients is associated with local bone defects due to marrow expansion and the appearance of extramedullary hematopoietic pseudotumors. It is also associated with several clinical sequelae due to the resulting anemia and iron overload. A hypercoagulable state due premature red cell death has also been described in this patient population, leading to frequent thrombotic and other vascular events [10].

Iron overload and its therapeutic targeting

Downregulated hepcidin and its subsequent impact on iron homeostasis results in increased iron absorption and a state of iron overload and ensuing oxidative stress. Primary disorders of iron overload include hereditary hemochromatosis (HH), the most common cause of which is mutations in the gene HFE. Beta thalassemia is also associated with iron overload due to hepcidin downregulation by ineffective erythropoiesis as stated earlier. Although iron loading from increased intestinal absorption in beta thalassemia is a slower than that secondary to regular transfusion therapy, it can still reach clinically significant thresholds associated with serious morbidity. Another iron overloading anemia that exhibits some hallmarks of ineffective erythropoiesis are autosomal recessive disorders caused by mutations in Codenin-1 and referred to as CDA-150. The factor GDF-15 that has been found to downregulate hepcidin in vitro, is upregulated in patients of both beta thalassemia and CDA-1, indicating that this factor might be an important biomarker of ineffective erythropoiesis and iron overload. The exact role of this factor ins ineffective erythropoiesis, if at all, remains debatable. Several avenues have been explored to target the ineffective erythropoiesis and iron overload in mouse models of non-transfusion dependent beta thalassemia. Given the significant role of TMPRSS6 in cleaving HAMP, genetic or pharmacological depletion of TMPRSS6 has been the subject of much study. Tmprss6−/− mice crossed with a mouse model of beta thalassemia intermedia (Hbb th3/+) resulted in improved splenomegaly, anemia and iron loading. Moreover, targeting Tmprss6 using siRNA and antisense oligonucleotides (ASO) significantly improved anemia and reduced hemichrome formation in Hbb th3/+ mice. Tmprss6 ASOs were also able to decrease serum iron transferrin saturation, liver iron accumulation in Hfe−/− mice exhibiting HH46. Additionally, minihepcidins which are small molecule agonists mimetic of HAMP activity and are capable of binding to and degrading FPN have also been used in preclinical studies of Hbb th3/+ mice showing amelioration of anemia and symptoms of ineffective erythropoiesis. The Minihepcidins, Tmprss6 ASO and Tmprss6 siRNA therapies have also been used in combination with treatment of the iron chelator deferiprone to target organ iron content under conditions of ameliorating ineffective erythropoiesis. Additional therapies that have also been in use involve administration of Apo transferrin in Hbb th3/+ as well as Hbb th1/th1 animals showing substantial fall in iron overload, hemichrome formation, and improvement of anemia. Other preclinical studies encompassing therapies to ameliorate ineffective erythropoiesis include the use of JAK2 inhibitors. Given the role of

the JAK2- STAT5 pathway in erythropoietin (EPO) production under hypoxic conditions and stress erythropoiesis, these seems to be an ideal possibility for therapeutic targeting. Indeed, use of JAK2 inhibitor in animals affected by beta-thalassemia show significant reduction of splenomegaly and improvement of anemia. Additionally, ligand traps based on the extracellular domains of activing receptors, such as RAP011 and RAP536 which target GDF11 have been shown to improve the erythroid precursor to mature RBC ratio in both Hbb th3/+ and Hbb th1/th1 animals, with amelioration of splenomegaly, anemia, and iron overloading conditions [11].

Iron metabolism and Regulation

Iron metabolism

The human body contains 3-4 grams of iron. The majority is utilized in erythrocytes to bind and shuttle oxygen throughout the body. Macrophages in the spleen, bone marrow, and liver recycle iron by taking up senescent erythrocytes and breaking them down to provide iron for processes such as erythropoiesis. The remaining iron is stored in hepatocytes, which serve as a regulatory unit to control the systemic iron level. An alternative regulatory measure to control body iron is adjusting its absorption realized by enterocytes in the duodenum. In enterocytes, iron is either stored to minimize the amount of circulating iron as ferritin or transported to the basal side and released into the bloodstream by Fpn, the only known iron exporter on a cellular level. After the release, iron is loaded onto transferrin and distributed safely throughout the body [12]. Transferrin bound iron is recognized by transferrin receptor (TfR), a membrane-bound protein that is widely expressed and commonly overexpressed on cells with a high iron demand, such as intermediate stages in red blood cell formation like erythroblasts. The regulation of systemic iron homeostasis is primarily executed by hepcidin, a 25 amino acid peptide. Hepcidin binds to Fpn, initiating the iron exporter's internalization and degradation and thereby decreasing available iron in the circulation. The expression of the HAMP gene, which encodes for hepcidin, is upregulated by a multitude of factors, including bone morphogenetic protein (BMP), hemojuvelin (HJV), and human hemochromatosis protein (HFE), targeting either the BMP receptor (BMPR) or the TfR on hepatocytes. Additionally, inflammatory cytokines such as interleukin 6 (IL-6) induce hepcidin biosynthesis and reduce plasma iron levels as a preventive measure against bacterial growth. To mobilize iron from its storages and increase its availability for processes like erythropoiesis, erythropoietin (EPO) stimulates erythroblasts to release the protein erythroferrone (ERFE), which inhibits hepcidin production by binding to BMPs. Elevated EPO production is observed under oxygen-deprived conditions, mediated by the hypoxia-inducible factor (HIF), which leads to increased downregulation of hepcidin and consequently promotes iron release. At the cellular level, non-protein-bound iron is presented as the labile iron pool, consisting of ferrous iron bound by low-affinity iron chelators. The labile iron pool regulates the intracellular iron flux via iron-responsive proteins (IRP) interacting with iron-responsive elements (IRE) and controlling the translation of mRNA encoding for ferritin, TfR1, Fpn, and divalent metal-ion transporter-1 (DMT1). Moreover, the transcription of TfR, DMT1, and Fpn is also controlled by HIF via binding to their hypoxia-responsive element (HRE), serving as a potent transcription factor. Prolyl-4-hydroxylase (PHD), which regulates the degradation of HIF, is highly Fe2+-dependent, making HIF and PHD suitable targets for the treatment of iron metabolism-related pathologies. Generally, iron homeostasis is affected by the disturbance of one or more of its key players, causing either an excess or a shortage of systemic iron [13]. Both conditions have detrimental effects on the overall health status of an individual.

Iron Regulation

Cellular Regulation of Iron-The Iron Regulating Proteins (IRPs)

Iron metabolism is regulated at both the systemic and cellular levels. In all vertebrates, the major protein involved in iron transport is TfR1. Differic-transferrin is taken up via the transferrin receptor. The Tf/TfR1 complexes are endocytosed through the clathrin-dependent pathway. Acidification within the endosome leads to a conformational change in Tf and TfR1, resulting in the dissociation of iron from Tf. After dissociation, the Tf-Tf1R complex is recycled back to the plasma membrane. The homologous protein of TfR1, transferrin receptor 2 (TfR2), is ubiquitously expressed in hepatocytes. At the cellular level, the regulation of the expression of proteins involved in iron metabolism and homeostasis, such as ferritin or the transferrin receptors, is coordinated through the interaction of iron sensing proteins, known as iron regulatory proteins (IRPs) or IRE-binding proteins, where IRE stands for iron-responsive elements. The IRE/IRP regulatory system was first described in the late 1980s. This network controls iron homeostasis by regulating gene expression post-transcriptionally. IREs are present in mRNA and are extremely conserved IRP binding sites, with a hairpin structure of 25–30 nucleotides, which are found in the untranslated region (UTR) of the mRNA transcripts encoding the H and L subunits of ferritin, in TFR1 as well as in several other genes related to iron metabolism. IRP1 and IRP2 are

homologous to the aconitase gene family, possessing the ability to sense cytosolic iron concentration and modify gene expression of their mRNA targets correspondingly. Thus, the IRP/IRE system is a key component for the organism, enabling the cells to rapidly accommodate cytosolic iron and facilitate the functioning of numerous iron-dependent cellular components at the post-transcriptional level [14].

Sensing and Regulating Intracellular Iron by IRP1 and IRP2

The intracellular iron pool regulates the binding of IRP1 and IRP2 to the IRE. IRP1 (90kDa) and IRP2 (105kDa) are RNA-binding proteins that interact with IRE to control the translation of ferritin and FPN mRNA and additionally control the stability of TfR mRNA. High iron levels, leading to the assembly of cubane clusters in IRP1, promote the inhibition of IRP1 binding activity to IRE, thereby leading to the conversion of IRP1 to aconitase. In iron starved cells, each IRP binds with high affinity to IREs. The translation of iron-related proteins is dependent on the location of the IRE on the UTR. IREs can be present either at 30 UTR or 50 UTR of the target mRNA. IRP prevents the translation of mRNA when binding to a single IRE located in the 50 UTR region, whereas the binding of IRP to IREs at the 30 UTR protects the transcript from endonucleolytic cleavage and degradation. For example, under low iron conditions, IRPs bind to IREs of the 50 UTR of FPN and ferritin mRNAs mediating their degradation, leading to a decrease in iron storage and export. However, simultaneously, the binding of the IRP's at the 30 UTR of TfR1 and DMT1 mRNAs will stabilize the transcripts, leading to increased iron import. In contrast, in iron-loaded cells, IRPs will not bind to the IREs located at the 50 UTR of transcripts, leading to their continuous translation. Conversely, transcripts possessing IREs at the 30 UTR will undergo endonuclease cleavage, leading to the subsequent degradation of the cleavage products [15].

Systemic Regulation of Iron -The Hepcidin–Ferroportin Axis

At the systemic level, iron homeostasis is regulated via the hepcidin-/ferroportin (FPN) axis. Hepcidin acts as a negative regulator of iron flows. FPN expression plays a crucial role in controlling iron release from enterocytes, liver hepatocytes and macrophages. FPN is composed of 12 transmembrane helices divided into two halves forming two lobes. The lobes can change between two conformational states. In the active first state, the central cavity is facing the intracellular space and is therefore not accessible from the outside. In the second conformational state, the cavity is open to the extracellular space and therefore no longer accessible from the intracellular side. In steady state conditions, iron is released from the main iron stores through FPN. For controlling plasma and tissue iron levels, FPN expression is tightly regulated at the posttranslational level by circulating hepcidin. Dysregulation of hepcidin expression results in iron disorders [16]. Hepcidin deficiency induces iron overload in hepatocytes such as in hereditary hemochromatosis. In contrast an overproduction of hepcidin is associated with iron-restricted anemia. Hepcidin is only regulated at the transcriptional level, mainly expressed in liver hepatocytes. The peptide undergoes proteolytic processing, leading to a bioactive molecule released into the bloodstream and there being able to bind and block FPN activity. Besides hepatocytes, monocytes, macrophages and the kidney are also able to produce hepcidin but to a lower extent. Binding of hepcidin to FPN expressed on macrophages, hepatocytes and other cell types induce internalization and lysosomal degradation of the iron exporter. Thus, iron export is blocked in FPN expressing cells, leading to cellular retention of iron. For example, in a situation of iron overload, hepcidin expression is increased, and iron-export through FPN is blocked. Thus, when a high level of iron in the circulation causes increased cellular uptake of iron, hepcidin expression is enhanced to prevent cellular export of iron to avoid systemic iron accumulation in the extracellular space. Hepcidin expression is inhibited under anemia or ineffective erythropoiesis but stimulated under a high iron load and inflammation. Additionally, it has been shown that ERFE is an important regulator of hepcidin expression and is needed for the rapid response to acute hemorrhage [17].

Regulation of Hepcidin through the Bone Morphogenetic Protein

Hepcidin expression is principally regulated transcriptionally by iron in a feedback loop involving multiple pathways by which hepatocytes recognize circulating iron status. The regulation of hepcidin synthesis is complex and involves several proteins present at the plasma membrane of hepatocytes, i.e., hereditary hemochromatosis proteins (HFE) and transferrin receptor 2 (TfR2) as well as hemojuvulin (HJV). They tightly regulate the expression level of hepcidin by the bone morphogenetic protein 6 (BMP-6). BMP-6 is an extracellular signaling molecule, belonging to the transformation growth factor (TGF-β) superfamily, expressed in hepatocytes. Elevated intracellular liver iron concentration enhances the expression of BMP6. Binding of BMP-6 to its corresponding BMP receptor (BMPR) and hemojuvelin (HJV), a BMP co-receptor, on hepatocytes, initiates intracellular signaling transduction via SMAD proteins. This pathway

involves phosphorylation of SMAD1, 5 and 8 (pSMADs) accompanied with pSMADs/SMAD4 translocating to the nucleus. This then activates the transcription expression of the hepcidin-encoding gene (HAMP). Serum iron levels may activate hepcidin expression autonomously of BMP6. Hepatocyte transferrin receptor 1 and 2 (TfR1, TfR2) and HFE function as extracellular iron sensors and specifically sense circulating concentrations of transferrin-bound iron. As HFE competes with Tf for binding to TfR1, HFE associates with TfR1 when serum iron levels are low and is displaced when the receptor binds Tf-Fe2. With increasing serum iron concentrations, Tf-Fe2 binds TfR1, leading to the displacement of HFE. The released HFE then interacts with TfR2. This HFE/TfR2 complex then interacts with hemojuvelin (HJV) and induces the BMP signaling pathway leading to hepcidin production (Figure 3). Similarly, to Hepcidin-deficiency, HFE deficiency causes hereditary hemochromatosis. As a consequence, loss of function of hemojuvelin, BMP6 and SMAD4 in knock-out mice leads to low hepcidin levels, resulting in iron overload, demonstrating the master regulatory role of hepcidin in iron homeostasis. Additionally, BMP-6 seems to be one of the major ligands responsible for the activation of hepcidin expression, as BMP-6 knockout mice showed a severe iron overload due to the failure to activate hepcidin expression [18].

Hepcidin Regulation by Inflammation

Inflammatory cytokine interleukin-6 (IL-6) can also trigger hepcidin induction via the IL-6R/STAT3 pathway. Inflammatory cytokines generated in the context of infections with iron-dependent invading pathogens, stimulate an innate immune response. This pathway is mediated by macrophages releasing IL-6 during infection and inflammation, leading to increased hepcidin levels, mediated by STAT3 signalling, resulting in iron sequestration. In more detail, IL-6 binds to the gp130 protein receptor complex mediating a JAK1/2 tyrosine-kinase-mediated phosphorylation of the transcription factor STAT3. When STAT3 is activated, it is translocated into the nucleus and binds to the STAT3-responsive element on the hepcidin promoter, leading to the induction of hepcidin transcription. STAT3 signalling therefore is an additional pathway to SMAD for stimulation of hepcidin production. Stimulation of hepcidin expression during an infection, induced via IL-6, greatly decreases the access of bioavailable iron to invading pathogens. Therefore, hepcidin expression and FPN degradation play a significant role in iron homeostasis and immunity. As a consequence of low extracellular iron levels due to hepcidin, pathogens, such as Yersinia pestis, the causative agent of the plague, produce potent iron chelators (siderophors) to overcome the scarcity of the metal [19].

Role of hepcidin and Inflammation

Inflammation and infection increase hepcidin synthesis. Patients with sepsis, inflammatory bowel disease, myeloma, burns, and C reactive protein (CRP) levels >10 mg/dL exhibit significantly elevated hepcidin levels. Macrophages are stimulated during the inflammatory process; the stimulation depends on the severity of inflammation. Activated macrophages release a network of cytokines. Among them is interleukin-6 (IL-6) is one of the primary inducers of hepcidin expression; an increase in hepcidin levels finally results in hypoferremia (Fig. 1). Hepcidin inhibits iron release from macrophages as well as intestinal iron absorption. In inflammatory states, hepcidin production is no longer regulated by iron burden (i.e., if the iron level is low, hepcidin synthesis should be downregulated) but is rather increased through IL-6 stimulation. Serum iron was demonstrated to affect hepcidin synthesis in healthy volunteers, in whom the early presence of hepcidin in the urine was measured after an oral iron administration dose that did not affect iron storage. Serum iron is an induction signal for hepcidin production and affects serum transferrin saturation percentage. In the case of inflammation, hepcidin can also be produced by myeloid cells via the activation of TRL4, a receptor located on the membranes of neutrophils and macrophages [20].

Prevalence in India

The prevalence data for anaemia in adults and children as reported by the Indian National Family Health Surveys NFHS-3 (2005–06), NFHS-4 (2015–16) and NFHS5 (2019–21) are summarised in Table 1. Overall, more than 58% of children aged 6–59 months were anaemic, with haemoglobin (Hb) concentrations of <11g/dL). Anaemia was more prevalent in children living in rural areas than urban areas, which is mainly related to mothers with little or no education and households of low wealth status. Rural children also suffer more undernutrition and are exposed to poorer sanitary conditions than urban children, which may lead to greater intestinal worm burdens. Also, children's anaemia status is closely linked to the anaemia status of the mother and early childbearing is most common in rural areas, with the likelihood that these mothers will be more anaemic than older urban mothers. Very similar findings have been seen in Africa, with rural Ethiopian children having a 23% greater risk of anaemia than urban children for similar reasons as seen in India [21].

It is concerning that the lower values seen in the 2015–16 survey compared with 2005–06 increased in 2019–21. The increases relative to 2015–16 were seen in mild (Hb 10.0–10.9 g/dL), moderate (Hb 7.0–9.9 g/dL) and severe anaemia (Hb < 7.0 g/dL), although the prevalence of severe and moderate anaemia remained lower that the values reported in NFHS-2 (1998–99). There was considerable variability in childhood anaemia between Indian states, with the highest prevalence in Gujarat (79.7%), followed by Jammu and Kashmir (72.7%) and Madhya Pradesh (72.7%), and the lowest seen in Kerala (39.4%). In addition, the number of states with anaemia prevalence greater than 60% doubled from 5 in 2015–16 to 11 in 2019–21. Singh et al. reported that the key factors responsible for the increased prevalence in 2019–21 included the low anaemia status of mothers and their socio-economic status and education. They also highlighted the need for more rigorous technology-based monitoring systems for food supplementation programmes in India to reduce the high prevalence of childhood anaemia. The overall prevalence of anaemia in women aged 15–48 years and men was also higher in those residing in rural areas than those in urban environments (Table 1). Anaemia rates for women in 2019–21 were mostly higher than for 2015–16, which supports the link with higher childhood prevalence in that period. There were also concerns that the higher anaemia rates seen in NFHS-5 (2019–21) were related to the use of capillary blood, which has been shown to give lower Hb values than venous blood. The current Diet and Biomarkers Survey in India (DABS-1) will use venous blood to measure Hb The study of Kumari et al. examined the cross-sectional prevalence of anaemia in 200 adolescent girls in a tertiary care hospital in Bihar in NE India. It found values broadly in agreement with NFHS-4, with 50% of girls aged 10–19 years being anaemic (Hb concentrations <12g/dL). The study highlighted the substantially increased need for dietary iron for adolescent girls, suggesting that they are particularly susceptible to IDA. A recent study analysed the data for 116,117 and 109,400 adolescent women (aged 15–19 years) obtained from NFHS-4 (2015–16) and NFHS-5 (2019–21), respectively, with the aim of identifying factors that contributed to a rise in adolescent anaemia in the second study compared with the first. In agreement with, it was concluded that target interventions for adolescent females were needed, especially in the states with the highest increase in anaemia prevalence. It also highlighted the importance of socioeconomic issues, such as wealth and education, as contributing to the risk of anaemia among adolescent women in India. In addition, it noted that poor nutritional status and adolescent motherhood are key risk factors for adolescent anaemia in this population. The study emphasises the urgency of a determined focused approach to reduce anaemia, particularly in this vulnerable section of the population. The study did reflect on the importance of low dietary intakes of iron, vitamin B12 and folate as contributors to anaemia, although it seems that data on the intake of these nutrients were not available for the subjects involved. Such data are clearly urgently needed, especially for female adolescents, but also for all sections of the population [22].

Prevention Strategies

Most anemias cannot be prevented. However, iron-deficiency and vitamin-deficiency anemia can be prevented by consuming the right diet, about which a dietician can guide you well.

Iron: Sources include red meat, dark-green leafy vegetables, beans and lentils, dried-fruits and iron-fortified cereals.

Folate/Folic acid: Sources include dark-green leafy vegetables, whole fruits or fruit juices, kidney beans, green peas, peanuts and fortified products such as bread, cereal, pasta and rice.

Vitamin B-12: Sources include dairy products, meat, soy products and fortified cereal.

Vitamin C: Sources include all citrus fruits – whole or juiced, strawberries, peppers, broccoli, melons and tomatoes. All of these help the body absorb iron better.

Dietary Diversification

Meat, fish, poultry, organ meat – heme iron

Green leafy vegetables, soya – non-heme iron

Combination can increase absorption

Heme iron increases bioavailability of nonheme iron

Vitamin C enhances iron absorption

Diverse foods include other key micronutrients – vitamin A, B12, folate

Diverse diets have numerous other benefits

Child growth • Immune function • Reduce consumption of unhealthy diet.

Supplementation and fortification

We estimated the cost-effectiveness of iron supplementation and iron fortification programs, each at geographic coverage levels of 50, 80, and 95%.

Iron supplementation

It is becoming increasingly clear that the main target group for iron supplementation should be all women of reproductive age, leading to adequate reserves for mother and foetus during pregnancy. In this analysis, iron supplementation involves the provision of iron to pregnant women during antenatal visits. The assumed dose follows WHO guidelines, with daily supplementation of 60 mg elemental iron given to pregnant women for 6 mo during pregnancy, and for 3 mo postpartum. The effectiveness estimates of iron supplementation interventions as applied in our analysis were based on a thorough review of the burden of disease attributable to iron deficiency by Stoltzfus et al. for the same world subregions as applied in the analysis. For the epidemiological subregion AfrD, for example, Stoltzfus et al. reported that iron deficiency contributes to 22% of all maternal mortality in women between 30 and 44 y, and to 33% of all perinatal mortality. For the purposes of this analysis, we therefore assumed that the maximum attainable health effects in women between 30 and 44 y of any iron supplementation intervention in subregion AfrD are an annual reduction of maternal mortality of 22% and of perinatal mortality of 33%. The effectiveness of iron supplementation intervention is reduced by the following: 1) the assumed suboptimal geographic coverage level, i.e., not all pregnant women receive iron supplementation; and 2) noncompliance to the full iron supplement regimen. Reasons for noncompliance with iron-deficiency treatment include inadequate program support (such as lack of financial support), insufficient service delivery (such as lack of supplies), and patient factors (such as misunderstanding instructions, side effects, or frustration about the frequency and the number of pills taken). Galloway and McGuire estimated that noncompliance reduces the number of women with sufficient iron intake and therefore the maximum attainable health effects of iron supplementation by 33% [23].

Iron fortification

Iron fortification involves the addition of iron, usually with folic acid, to an appropriate food vehicle that is made available to the population at large. Cereal flour is the most common food vehicle but others, such as noodles, rice, and various sauces, have also been used. The present CEA is based on the addition of elemental iron powders to cereal flours. Elemental iron powders have been used for this purpose for 50 y and continue to be the most widely used iron compound. They have the advantage of causing few, if any, color and flavor problems in stored food vehicles. They are inexpensive and suitable for fortification of staple foods, such as wheat flour and maize flour. The analysis is based on the use of electrolytic iron (45 m, 325 mesh) of which evidence suggests that it should be a useful iron fortification. There have been very few trials of either efficacy or effectiveness of iron fortification for improving iron status. In industrialized countries with high bioavailability diets, this strategy has been assumed to have a beneficial effect on iron status. In populations consuming low bioavailability diets, such as those consumed in many developing country contexts, there is some evidence of benefit, as reviewed by Allen and Gillespie and also suggested in recent studies. However, the benefit may be much less, and much greater amounts of fortification may have to be added. For that reason, the maximum attainable health effects of fortification were considered to be only 50% of those of supplementation (personal communication, R. Stoltzfus, Cornell University). As in iron supplementation, the effectiveness of iron fortification at the population level was further reduced for two reasons. Firstly, we explored the costs and effects in the event that fortification reaches various suboptimal geographic coverage levels. Second, within these coverage levels, only a limited proportion of the population consumes the food vehicle in sufficient quantities to absorb sufficient iron levels of the targeted population [24].

Infection Control and Deworming

Soil-transmitted helminth infections are among the most common infections in humans, caused by a group of parasites commonly referred to as worms, including roundworms, whipworms and hookworms. Those living in poverty are most vulnerable to infection which can impair nutritional status by causing:

Internal bleeding which can lead to loss of iron and anaemia; Intestinal inflammation and obstruction; Diarrhoea; and

Impairment of nutrient intake, digestion and absorption. Evidence shows that preventive chemotherapy, or the periodic large-scale administration of anthelminthic medicines to populations at risk, can dramatically reduce the burden of worms caused by soil-transmitted helminth infections.

Preventive chemotherapy is an important part of a comprehensive package to eliminate morbidity due to soil-transmitted helminths in at-risk populations. However, long-term solutions to soil-transmitted helminth infections will need to address many factors, including improvements in water, sanitation and hygiene. Preventive chemotherapy (deworming), using annual or biannuala single-dose albendazole (400 mg) or mebendazole (500 mg)b is recommended as a public health intervention for all young children 12–23 months of age, preschool children 1–4 years of age, and school-age children 5–12 years of age (in some settings up to 14 years of age) living in areas where the

baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminth infection.

a. Biannual administration is recommended where the baseline prevalence is more than 50%.
b. A half-dose of albendazole (i.e. 200 mg) is recommended for children younger than 24 months of age.

Maternal and Adolescent Health Programs

India is home to the world's largest adolescent population. It also leads one of the most ambitious public health campaigns against anemia, a condition that continues to affect millions, especially women, children, and adolescents. Anemia, primarily caused by iron deficiency, results from low haemoglobin levels, reducing the blood's capacity to carry oxygen to vital organs. Deficiencies in folate, vitamin B12, and vitamin A are other nutritional causes of anemia. Its widespread prevalence is rooted in poor nutrition, early pregnancies, inadequate maternal care, and limited access to iron-rich foods, making it a pressing public health challenge that demands urgent and sustained action [25]. Anemia is both preventable and treatable, and over the past two decades, the Government of India has taken strong, targeted action to combat it. A significant turning point came with the Second National Family Health Survey (NFHS-2) in 1998–99, paving the way for landmark programs like Anemia Mukt Bharat (AMB). Today, AMB reaches millions annually through a comprehensive strategy that includes Iron-Folic Acid supplementation, deworming, fortified nutrition, and behaviour change communication across all age groups [26-28]. By integrating maternal and child health with adolescent nutrition and school-based outreach, India is actively disrupting the intergenerational cycle of malnutrition. This sustained, community-led approach transforms outcomes for girls, pregnant and lactating women, and children under five—positioning India as a global leader in evidence-based, inclusive public health innovation [29-31].

Self-Care and Lifestyle Measures

Self-Care

There are several ways to help prevent and manage anaemia in daily life, including eating a healthy and diverse diet and speaking to a health-care provider early if you have symptoms of anaemia.

To keep a healthy and diverse diet:

Eat iron-rich foods, including lean red meats, fish and poultry, legumes (e.g. lentils and beans), fortified cereals and dark green leafy vegetables;

Eat foods rich in vitamin C (such as fruits and vegetables) which help the body absorb iron; and

Avoid foods that slow down iron absorption when consuming iron-rich foods, such as bran in cereals (wholewheat flour, oats), tea, coffee, cocoa and calcium.

If you take calcium and iron supplements, take them at different times during the day.

People with heavy menstrual bleeding should see their doctor for treatment. Doctors may recommend iron supplements or hormonal contraceptives. Some infections can cause anaemia. Wash your hands with soap and water and use clean toilets to reduce the risk of infection. Malaria can also cause anaemia. People living in places where malaria is common should follow prevention advice from local health authorities. Seek prompt treatment if you suspect you have malaria.

Lifestyle

Iron-Rich Diet

Begin by embracing a diet rich in iron, a key nutrient essential for red blood cell production. Include leafy greens, lean meats, legumes, and fortified cereals in your meals. Pairing iron-rich foods with sources of vitamin C enhances iron absorption, optimizing its effectiveness.

Mindful Stress Management

Chronic stress can contribute to anemia and exacerbate its symptoms. Incorporate stress-reducing activities such as meditation, yoga, or deep breathing exercises into your daily routine to promote overall well-being and support your body's ability to manage anemia effectively.

Hydration Matters

Staying adequately hydrated is crucial for overall health and can positively impact anemia. Water supports the circulatory system, ensuring that red blood cells can efficiently transport oxygen throughout the body. Drinking water can also reduce the risk of kidney stone and other complications.

Supplementation

In consultation with healthcare professionals, consider incorporating iron supplements into your routine. This can be particularly beneficial for individuals with difficulty obtaining sufficient iron from their diet or those with chronic conditions affecting iron absorption.

Conclusion

Anemia, especially iron deficiency anemia, remains one of the most persistent and multifaceted public health challenges globally, with particularly severe consequences for vulnerable populations in India. The findings of this thesis underscore that anemia is not merely a biomedical condition, but a social indicator of deep-rooted inequalities spanning nutrition, sanitation, education, and healthcare access. The examination of various types of anemia—nutritional and non-nutritional—revealed distinct etiological mechanisms involving deficiencies in iron, vitamin B_{12}, and folate, alongside infectious contributors such as malaria, tuberculosis, and HIV/AIDS. These are compounded by gender-based disparities, cultural norms, and socioeconomic challenges that disproportionately affect children under five, adolescent girls, and pregnant women. The alarming prevalence rates reported in NFHS surveys, particularly in Bihar, emphasize the need for urgent and tailored responses. Beyond its clinical manifestations, anemia significantly impairs cognitive and physical development, reduces economic productivity, and contributes to maternal and perinatal mortality. Its economic ramifications include increased healthcare costs and measurable losses to national GDP—transforming it into a broader developmental and policy issue. Effective anemia control requires a multisectoral approach. This includes micronutrient supplementation, dietary diversification, deworming, improved maternal-child care, and gender-sensitive strategies. Policy innovations such as delayed cord clamping, breastfeeding promotion, adolescent health education, and maternal nutrition support have shown promise in pilot initiatives. However, success hinges on sustained intersectoral collaboration, community participation, robust data systems, and education.

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Conflict of Interest

None declared.

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