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REVIEW ARTICLE

REPROGRAMMING IRON METABOLISM IN HIV: MOLECULAR MECHANISMS DRIVING VIRAL PERSISTENCE AND DISEASE PROGRESSION

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Abstract

Iron, an essential micronutrient, serves multiple functions in the development of Human Immunodeficiency Virus (HIV) infection, affecting viral replication, immune responses, and the advancement of the disease. This analysis explores the detailed molecular dynamics of iron management in HIV infection, illuminating the intricate relationship between iron metabolism and viral development. This review investigates the molecular mechanisms related to iron dysregulation in individuals with HIV, clarifying the effects of disrupted iron homeostasis on disease advancement and pinpointing possible therapeutic targets. Iron balance is closely controlled in the body, with disturbances linked to the development of several diseases, such as HIV infection. HIV affects iron metabolism in various ways, impacting both host and viral functions. Iron accumulation, frequently seen in individuals infected with HIV, has been linked to faster disease progression, immune impairment, and higher mortality rates. On the other hand, a lack of iron can weaken immune response and worsen complications related to HIV. Changes in iron balance significantly impact the progression of HIV and its clinical results. Iron imbalance can promote viral reproduction, worsen immune dysfunction, and intensify HIV-related comorbidities such as heart disease, cognitive decline, and anemia. Moreover, oxidative stress and inflammation triggered by iron lead to tissue harm and systemic issues, which further worsen HIV pathogenesis. Clarifying the molecular dynamics of iron orchestration in HIV infection offers important insights into disease mechanisms and reveals possible targets for therapeutic intervention.
Keywords: Molecular dynamics, iron, HIV, disease progression.

INTRODUCTION

Iron is a vital element for nearly all living organisms because of its important function in numerous cellular processes, such as DNA synthesis, oxygen transport, and energy production. The intricate equilibrium of iron in the body is upheld by a complex system of proteins and hormones that control its absorption, storage, and use. This precisely adjusted system guarantees that iron is accessible for essential cellular functions while avoiding the harmful consequences of excessive iron. Nevertheless, disturbances in iron balance can lead to serious pathological outcomes, particularly regarding infectious diseases like Human Immunodeficiency Virus (HIV) infection[1]. HIV, which is responsible for acquired immunodeficiency syndrome (AIDS), continues to be a worldwide health emergency despite major progress in antiretroviral therapy (ART). The virus assaults and reduces CD4+ T lymphocytes, resulting in immunodeficiency and heightened vulnerability to opportunistic infections and specific cancers[2]. Grasping the intricate relationships between HIV and host cell processes is vital for creating successful treatments and interventions. A developing area of interest is the significance of iron metabolism in the pathogenesis of HIV, since iron is crucial for both the immune function of the host and the lifecycle of the virus[3].

Iron balance is regulated by essential proteins like transferrin, ferritin, and hepcidin. Transferrin carries iron in the blood, supplying it to cells through the transferrin receptor. Ferritin contains iron in cells and releases it in a regulated way when required. Hepcidin, a hormone produced by the liver, controls iron release from cells by attaching to ferroportin and facilitating its degradation, which is the only recognized iron exporter in mammals. Imbalance of these proteins may result in either iron deficiency or iron excess, both associated with negative consequences in individuals infected with HIV. In the scenario of HIV infection, iron metabolism

is closely connected to viral replication and immune reactions. The replication of HIV necessitates iron-dependent enzymes, including reverse transcriptase and integrase. Increased iron concentrations in host cells can boost viral replication, whereas chelating iron has been demonstrated to impede these activities. This reliance on iron for viral replication highlights the possibility of focusing on iron metabolism as a treatment approach for HIV[4].

Iron affects the activity of different immune cells, such as macrophages and T-lymphocytes. Macrophages, crucial for iron recycling, can be manipulated by HIV to establish an iron-rich setting that promotes viral endurance. Iron accumulation can affect T-lymphocyte function, thus diminishing the immune response and promoting HIV advancement.[5-6] Oxidative stress and inflammation also contribute to HIV pathogenesis, with iron being a crucial factor. Iron promotes the generation of reactive oxygen species (ROS), resulting in oxidative stress that harms cellular structures and intensifies inflammation. Persistent oxidative stress and inflammation are defining characteristics of HIV infection and aid in the advancement to AIDS. This oxidative setting can additionally weaken immune response and enhance viral replication.[7-8] The possible therapeutic benefits of focusing on iron metabolism in HIV infection are considerable. Iron chelation therapy, by lowering the availability of iron for viral replication, has demonstrated potential in experimental research. Nonetheless, meticulous oversight is necessary to prevent negative impacts linked to iron deficiency in the host[9,10]. Regulating the function of iron-related hormones like hepcidin and ferroportin offers a new therapeutic strategy, potentially returning iron homeostasis to normal levels and decreasing complications associated with HIV. Furthermore, alongside direct iron regulation, antioxidant treatments might alleviate certain oxidative damage caused by iron during HIV infection[11].

The aim of this article is to provide a comprehensive overview of iron utilization and storage in the human body, highlighting the importance of maintaining balanced iron levels for optimal health.

Iron homeostasis in health

Iron is a vital micronutrient important for many physiological functions, such as oxygen transport, DNA synthesis, and electron transport within mitochondria. Keeping iron balance is essential since both a lack of iron and an excess of iron can lead to serious health issues. The body manages iron levels via a sophisticated system of proteins that oversee iron intake, movement, storage, and reuse[12,13]. Iron intake mainly takes place in the duodenum and upper jejunum of the small intestine. Iron in the diet comes in two varieties: heme iron, which is present in animal foods, and non-heme iron, which is located in plant foods. Heme iron is absorbed more effectively than non-heme iron. Upon reaching the intestinal lumen, heme iron enters enterocytes directly, whereas non-heme iron needs to be reduced from its ferric (Fe^{3+}) to ferrous (Fe^{2+}) state by a reductase enzyme prior to absorption via the divalent metal transporter 1 (DMT1). After absorption, iron needs to be securely delivered to different body tissues[14,15]. Inside enterocytes, iron may be retained in ferritin or released into the bloodstream via ferroportin, the sole identified iron exporter. Hepcidin, a hormone produced by the liver, regulates ferroportin's activity. Hepcidin attaches to ferroportin, leading to its internalization and degradation, which decreases iron export from enterocytes, macrophages, and hepatocytes[16].

Iron that the body doesn't use right away is mainly stored in the liver, spleen, and bone marrow. Ferritin, a protein found within cells, holds iron in a safe, soluble state and liberates it when required. Every ferritin molecule has the capacity to hold as many as 4,500 iron atoms. Hemosiderin, another iron storage protein, has lower solubility and is commonly present in iron overload conditions[17]. The body recycles iron from aged red blood cells (RBCs) via macrophages located in the spleen and liver. These macrophages engulf aged RBCs, decomposing hemoglobin to free iron, which is subsequently either stored or returned to circulation for reuse. This recycling procedure is very effective, fulfilling a large portion of the body's daily iron requirements and decreasing dependence on iron from food. Iron balance is closely monitored to avoid both a deficiency and excess[18,19]. Hepcidin is pivotal in this regulation. When body iron stores are adequate or during inflammation, hepcidin concentrations rise, decreasing iron absorption and encouraging iron retention within cells. On the other hand, when iron levels are deficient or erythropoiesis is elevated, hepcidin levels drop, promoting iron absorption and release from reserves. Iron regulatory proteins (IRPs) also play a role in sustaining iron equilibrium at the cellular level. IRPs attach to iron-responsive elements (IREs) on mRNAs that code for proteins related to iron metabolism, like transferrin receptor and ferritin[20-23].

Iron utilization and storage

Iron is a crucial micronutrient required for many biological functions, such as oxygen transport, energy generation, and DNA synthesis. The body meticulously manages iron usage and storage to ensure optimal cellular function and to avoid iron excess, which can cause oxidative damage and harm to tissues. Grasping the processes of iron use and storage is essential for recognizing its significance in health and illness[24,25]. The main role of iron in the body is to create hemoglobin, the protein found in red blood cells (RBCs) that transports oxygen from the lungs to other tissues in the body. Iron is integrated into heme, a part of hemoglobin, during erythropoiesis, the process of red blood cell production. Erythroid precursors in the bone marrow need enough iron for hemoglobin synthesis, which guarantees proper oxygen transport to tissues[26,27]. Iron plays a vital role in the electron transport chain, a sequence of protein complexes found in the inner mitochondrial membrane that produce adenosine triphosphate (ATP), the main energy currency of cells. Proteins that contain iron, like cytochromes and iron-sulfur clusters, promote electron transfer among complexes, fueling ATP production via oxidative phosphorylation. Iron acts as a cofactor for numerous enzymes crucial for vital metabolic

functions, such as DNA synthesis, cellular respiration, and defense against oxidative stress[28,29].

Surplus iron that is not instantly required for cellular functions is mainly stored as ferritin, a cytosolic protein complex present in nearly all cells. Ferritin functions as a safeguard against variations in intracellular iron concentrations, storing surplus iron in a non-harmful, soluble state. Ferritin molecules are composed of a shell made of heavy (H) and light (L) chains that encase iron atoms in its core[30,31]. In cases of extended iron overload, ferritin can reach saturation, resulting in the creation of hemosiderin, an iron storage complex that is less soluble. Hemosiderin aggregates are commonly found in tissues such as the liver, spleen, and bone marrow, and represent a long-term iron reservoir. Although hemosiderin offers increased storage potential, its buildup may signal medical issues like hemochromatosis or multiple blood transfusions[32,33]. Iron usage and storage are closely controlled to ensure iron balance and avoid both deficiency and excess. Cellular iron absorption is regulated by the transferrin-transferrin receptor mechanism, which oversees the entry of transferrin-bound iron into cells through receptor-mediated endocytosis[34,35].

Altered iron metabolism in HIV

HIV infection causes a range of changes to iron metabolism, upsetting the delicate balance maintained in healthy people. These alterations go beyond the commonly acknowledged hematological effects linked to HIV, like anemia, including a complicated interaction of molecular occurrences that affect systemic iron levels, their distribution, and regulatory processes[36]. HIV infection frequently causes variations in systemic iron levels. Some individuals might face a reduction in iron levels, leading to anemia, while others could show increased iron levels, possibly linked to inflammatory processes. The factors influencing these fluctuations are complex and include the interaction between viral replication, immune response, and changes in iron balance[37]. The prolonged immune response typical of HIV infection plays a key role in changed iron metabolism. Pro-inflammatory cytokines like interleukin-6 (IL-6) are involved in the upregulation of hepcidin. Hepcidin, consequently, restricts iron export via ferroportin, resulting in the retention of iron inside macrophages and hepatocytes. This redistribution of iron plays a role in the anemia of chronic disease seen in individuals with HIV[38]. HIV directly affects iron metabolism, impacting both viral replication and the responses of host cells[39].

Inflammation and immune activation caused by HIV lead to oxidative stress, fostering conditions that promote iron overload. High iron levels, along with heightened reactive oxygen species, can result in cellular damage and foster the development of complications linked to HIV. Hepcidin, an essential regulator of iron balance, is affected by both HIV and the related inflammation. The dysregulation that results leads to iron sequestration in cells, affecting erythropoiesis and worsening anemia in individuals with HIV. Altered iron metabolism in HIV has clinical consequences that go beyond just hematological issues[40-43].

Iron and immune response in HIV

The connection between iron and the immune response regarding HIV is a complex interaction that greatly affects the development and results of the infection. Iron, an essential micronutrient, has a dual function in immune response, serving as a crucial cofactor for numerous cellular activities while also presenting potential risks when not properly regulated during HIV infection. Iron is required for the optimal functioning of immune cells such as T lymphocytes, B lymphocytes, and macrophages[44]. These cells need iron for functions like DNA synthesis, energy generation, and cell division. The delicate equilibrium of iron availability is vital, as surplus iron may cause oxidative stress and harm, affecting immune cell survival and performance[45]. T lymphocytes, key components of the adaptive immune response, are affected by iron levels. A deficiency in iron can hinder T cell growth and activity, weakening the body's capability to initiate a robust immune response to HIV. Conversely, high levels of iron may lead to oxidative stress, which can hinder T cell function[46]. Macrophages, essential elements of the innate immune system, are vital for recycling iron from aging red blood cells. Nonetheless, within the framework of HIV, disrupted iron metabolism can influence macrophage activity[47].

The persistent immune activation seen in HIV infection leads to inflammation, which also affects iron dynamics. Cytokines involved in inflammation, like interleukin-6 (IL-6), can trigger the production of hepcidin, resulting in reduced iron absorption and storage in macrophages. This iron redistribution plays a role in the anemia of chronic disease observed in individuals with HIV[48]. Iron serves as a modulator of immune activation, influencing the equilibrium between pro-inflammatory and anti-inflammatory responses. Imbalanced iron levels can disrupt this equilibrium, potentially worsening immune dysfunction in HIV by fostering a setting that encourages ongoing inflammation[49]. Adjusting iron levels might serve as a potential intervention approach, focused on restoring immune cell activity and alleviating the negative impacts of disrupted iron metabolism on the immune system[50]. The interaction between iron and the immune response in HIV is a key factor in disease advancement[51].

Oxidative stress and iron overload in HIV

Oxidative stress and excess iron present related issues in the context of HIV infection, leading to a complex interaction of molecular processes that influence disease progression and related complications[52]. This complex connection encompasses a two-way influence, with HIV-related inflammation resulting in oxidative stress and subsequent iron accumulation, fostering an environment favorable to cellular harm and immune impairment. Chronic immune activation and inflammation are defining characteristics of HIV infection. The continual activation of the immune system leads to the production of pro-inflammatory cytokines and reactive oxygen species (ROS)[53]. This inflammatory setting generates oxidative stress, a state

marked by the imbalance between ROS production and the body's capacity to counteract them. Oxidative stress, worsened by HIV-related inflammation, leads to cellular harm. Increased ROS levels lead to lipid peroxidation, oxidation of proteins, and damage to DNA. This cellular harm affects the functionality and survival of immune cells, possibly undermining the host's capacity to launch a strong defense against the virus[54]. Iron accumulation, commonly seen with HIV, further intensifies oxidative stress[55].

Immune cells, such as T lymphocytes and macrophages, are especially vulnerable to the harmful impacts of oxidative stress and excessive iron[56]. Oxidative harm can disrupt immune cell functionality, interfere with signaling pathways, and lead to apoptosis, ultimately impacting the general immune reaction to HIV. Oxidative stress and excess iron are involved in the advancement of HIV-related complications. The combined effects of neurocognitive disorders and cardiovascular complications go beyond the conventional view of HIV solely as an immunodeficiency disorder[57]. Understanding the interconnectedness of oxidative stress and iron overload creates opportunities for treatment approaches. Approaches designed to regulate iron levels, enhance antioxidants, and address inflammatory pathways may offer potential in alleviating the negative impacts of these interrelated processes and enhancing overall patient outcomes in HIV[58]. Oxidative stress and excess iron represent complex components of HIV pathogenesis, forming a difficult environment that affects immune function and aids in the advancement of related complications[59].

Iron as a co-factor for HIV replication

Iron serves as a crucial co-factor for various enzymes involved in cellular processes, and its role in HIV replication adds a layer of complexity to the interplay between the virus and host cell machinery. Understanding how iron functions as a co-factor for HIV replication provides insights into potential targets for therapeutic interventions[60]. HIV replication involves several iron-dependent enzymes critical for different stages of the viral life cycle. One notable example is the ribonuclease H (RNase H) enzyme, which is essential for viral reverse transcription. Iron is a cofactor for the activity of RNase H, facilitating the cleavage of RNA strands in the viral RNA-DNA duplex[61]. During the early stages of HIV infection, the viral RNA genome is reverse transcribed into DNA by the viral reverse transcriptase enzyme. The activity of reverse transcriptase, in part, relies on the presence of iron. Optimal iron levels facilitate efficient reverse transcription, a pivotal step in the establishment of viral DNA within the host cell[62]. Integrase is another key enzyme in HIV replication, responsible for integrating the viral DNA into the host cell genome. Iron may play a regulatory role in the activity of integrase, influencing the efficiency of this integration process. This step is critical for the establishment of a persistent viral reservoir[63].

The availability of iron within the cellular environment can influence the overall fitness of the virus. Iron scarcity may lead to suboptimal activity of iron-dependent enzymes, potentially affecting the efficiency of viral replication. Conversely, iron abundance could enhance viral replication, contributing to increased viral load[64]. Recognizing the dependence of HIV on iron for certain enzymatic activities opens avenues for therapeutic intervention. Modulating iron availability or targeting iron-dependent viral enzymes could be explored as strategies to disrupt the viral life cycle and reduce the replication of HIV within host cells[65]. Iron chelation, a process of binding and removing excess iron from the cellular environment, has been investigated as a potential antiviral strategy. By limiting the availability of iron, this approach aims to interfere with the co-factor function of iron for viral enzymes, potentially impeding HIV replication[66]. The role of iron as a co-factor for HIV replication highlights the intricate relationship between host cell metabolism and viral dynamics[67].

Iron-mediated inflammation in HIV

Iron-mediated inflammation plays a significant role in the complex pathogenesis of HIV, contributing to the chronic immune activation and dysregulation characteristic of the infection. The interplay between iron and inflammation creates a feedback loop that influences disease progression, immune dysfunction, and the development of HIV-associated complications[68]. Hepcidin, a key regulator of iron homeostasis, is intricately linked to inflammation. In response to inflammatory signals, such as interleukin-6 (IL-6), hepcidin production increases. Elevated hepcidin levels, in turn, lead to the internalization and degradation of ferroportin, reducing iron export from macrophages and enterocytes. This contributes to iron sequestration within cells and further exacerbates the anemia of chronic disease observed in HIV[69]. Macrophages, central players in the immune response, are involved in iron recycling and can contribute to iron-mediated inflammation. HIV-induced immune activation stimulates macrophages to release pro-inflammatory cytokines, creating an environment conducive to hepcidin upregulation and alterations in iron metabolism[70]. Iron-mediated inflammation is closely linked to oxidative stress. Excessive iron levels, particularly in the presence of inflammation, can contribute to the generation of reactive oxygen species (ROS). This oxidative stress further amplifies inflammatory responses, creating a cycle of cellular damage and immune dysregulation[71].

Iron-mediated inflammation can impact the function of immune cells, including T lymphocytes. Chronic inflammation and alterations in iron metabolism may contribute to immune exhaustion, impaired responsiveness, and compromised antiviral activity. This has implications for the overall effectiveness of the immune response against HIV[72]. Iron-mediated inflammation is implicated in the progression of HIV-associated complications, including cardiovascular diseases, neurocognitive disorders, and metabolic abnormalities. The chronic inflammatory state, influenced by iron dysregulation, contributes to the development and exacerbation of these comorbidities[73]. Understanding the role of iron-mediated inflammation in HIV opens avenues for therapeutic interventions.

Modulating iron metabolism or targeting inflammatory pathways may represent strategies to mitigate the adverse effects of chronic inflammation, potentially improving overall health outcomes in individuals living with HIV[72]. Iron-mediated inflammation adds a layer of complexity to the immunopathogenesis of HIV. The intricate interplay between iron dysregulation and inflammatory responses contributes to the chronic immune activation observed in HIV-positive individuals. Investigating these interactions provides insights into potential therapeutic targets for managing inflammation and improving the overall health of individuals living with HIV[74].

Molecular dynamics of iron orchestration in HIV infection

Human Immunodeficiency Virus (HIV) infection remains a global health concern despite advances in treatment and prevention strategies. Understanding the intricate molecular mechanisms underlying HIV pathogenesis is crucial for developing effective therapeutic interventions. Iron, an essential micronutrient, has emerged as a significant player in the complex interplay between the virus and the host immune system. This review delves into the molecular dynamics of iron orchestration in HIV infection, exploring its implications for disease progression and therapeutic targeting[75]. Iron metabolism is tightly regulated in the body to ensure optimal cellular function while preventing toxicity. In the context of HIV infection, alterations in iron homeostasis have been observed. The virus exploits host iron metabolism to support its replication and evade immune surveillance. Elevated iron levels within host cells create an environment conducive to viral replication, while iron deficiency compromises immune function, exacerbating disease progression[76]. Iron modulation in Human Immunodeficiency Virus (HIV) infection involves a complex interplay between the virus and the host's iron metabolism machinery. Understanding the molecular mechanisms underlying iron modulation is crucial for deciphering its role in HIV pathogenesis and identifying potential therapeutic targets. HIV exploits host iron uptake and transport mechanisms to ensure an adequate supply of iron for its replication. The virus upregulates expression of transferrin receptor 1 (TfR1), the primary receptor for cellular iron uptake, thereby increasing iron acquisition by infected cells. Additionally, HIV-infected cells may release exosomes containing ferritin, a protein that stores iron, facilitating its uptake by neighboring cells and promoting viral replication.

Hepcidin, a liver-produced peptide hormone, plays a central role in regulating systemic iron homeostasis by controlling the expression of ferroportin, the sole known iron exporter. In HIV infection, hepcidin levels are dysregulated, leading to alterations in iron distribution and availability. HIV-induced inflammation stimulates hepcidin expression, resulting in ferroportin degradation and intracellular iron retention. This iron sequestration promotes viral replication by providing a reservoir of iron for the virus[77]. Iron-sulfur clusters (Fe-S clusters) are essential cofactors for numerous cellular proteins involved in DNA repair, mitochondrial respiration, and iron metabolism. HIV exploits host Fe-S cluster biogenesis machinery to support viral replication. The virus may hijack iron-sulfur cluster assembly pathways to generate Fe-S clusters required for the activity of viral enzymes, such as reverse transcriptase and integrase, thereby enhancing viral replication efficiency. Iron dysregulation in HIV infection contributes to oxidative stress and chronic inflammation, further exacerbating disease progression. Elevated iron levels promote the generation of reactive oxygen species (ROS) through Fenton and Haber-Weiss reactions, leading to oxidative damage to cellular macromolecules. Additionally, iron-induced inflammation activates immune cells, such as macrophages and T lymphocytes, exacerbating tissue injury and immune dysfunction[78]. Iron dysregulation in HIV infection impairs immune function, contributing to disease progression and susceptibility to opportunistic infections. Iron overload compromises the function of immune cells, such as macrophages and T lymphocytes, impairing their ability to mount an effective antiviral response. Conversely, iron deficiency diminishes immune cell proliferation and cytokine production, further weakening the host immune response to HIV and other pathogens.

Implications for disease progression

The dysregulation of iron metabolism in Human Immunodeficiency Virus (HIV) infection has profound implications for disease progression, influencing various aspects of pathogenesis and clinical outcomes. Iron dysregulation promotes viral replication by providing a favorable environment for HIV proliferation within host cells. Elevated iron levels enhance the activity of iron-dependent viral enzymes, such as reverse transcriptase and integrase, leading to increased viral replication rates. Consequently, higher viral loads are associated with more rapid disease progression and increased severity of HIV-related complications[79]. Iron dysregulation compromises immune function, impairing the host's ability to mount an effective antiviral response and increasing susceptibility to opportunistic infections. Iron overload suppresses immune cell function, inhibiting the proliferation and activity of macrophages, T lymphocytes, and natural killer cells. This immune dysfunction predisposes individuals to infections with opportunistic pathogens, such as Mycobacterium tuberculosis and Pneumocystis jirovecii, contributing to disease progression and morbidity in HIV-infected individuals. Iron dysregulation in HIV infection contributes to oxidative stress and chronic inflammation, exacerbating tissue damage and immune dysregulation. Elevated iron levels promote the generation of reactive oxygen species (ROS), leading to oxidative damage to cellular components and tissues. Additionally, iron-induced inflammation activates immune cells and pro-inflammatory cytokines, perpetuating a cycle of tissue injury and immune dysfunction. Chronic oxidative stress and inflammation are hallmarks of HIV infection and contribute to the progression of acquired immunodeficiency syndrome (AIDS) and the development of HIV-related comorbidities. Iron dysregulation is associated with an

increased risk of developing HIV-related comorbidities, such as cardiovascular disease, neurocognitive disorders, and metabolic abnormalities. Iron overload promotes the development of atherosclerosis and cardiovascular complications through oxidative stress-mediated endothelial dysfunction and lipid peroxidation. Furthermore, iron-induced neuro-inflammation and oxidative stress contribute to the pathogenesis of HIV-associated neurocognitive disorders (HAND). These comorbidities contribute to increased morbidity and mortality among HIV-infected individuals, highlighting the importance of addressing iron dysregulation in HIV care[79].

Individual peculiarities that may have an impact on iron metabolism

Iron metabolism is a highly regulated process that can be influenced by various factors, including genetic variations, the presence of infections like HIV, and individual responses to antiretroviral therapy (ART). Below are detailed explanations of the individual peculiarities that may impact iron metabolism, particularly in the context of HIV infection.

1. Genetic Variations

Genetic variations can influence the expression of genes involved in iron metabolism. For instance, Single Nucleotide Polymorphisms (SNPs) in the HAMP gene, which encodes hepcidin, can lead to variations in hepcidin levels. Individuals with certain SNPs may experience higher or lower hepcidin expression, affecting iron absorption and distribution. Variations in genes that code for transferrin (TF) and ferritin (FTH1) can impact how efficiently iron is transported and stored. For example, polymorphisms in the TF gene may alter transferrin levels, influencing iron bioavailability and leading to conditions such as iron overload or deficiency. Genes that regulate the immune response can also affect iron metabolism. Variations in cytokine genes (e.g., IL-6, TNF-α) can modify inflammatory responses, which in turn influences hepcidin levels. Elevated levels of these cytokines in HIV infection can result in increased hepcidin, leading to iron sequestration and anemia[78].

Host Factors Influencing Iron Metabolism

Age and Sex

Age and sex can significantly influence iron metabolism. For instance, premenopausal women generally have lower iron stores than men due to menstrual blood loss. Age-related factors, such as hormonal changes and dietary habits, can also impact iron absorption and metabolism[79].

Nutritional Status

The nutritional status of an individual plays a crucial role in iron metabolism. Deficiencies in micronutrients (e.g., vitamin C, vitamin A, and B vitamins) can impair iron absorption and utilization. Conversely, excessive dietary iron intake can lead to iron overload, especially in individuals with genetic predispositions to high iron absorption[78].

Comorbidities

Co-existing health conditions can also impact iron metabolism. Conditions such as chronic kidney disease, liver disease, and inflammatory disorders can alter iron regulation. For example, chronic inflammation can lead to anemia of inflammation, characterized by increased hepcidin levels and decreased iron availability.

HIV-Specific Factors

Viral Load and Immune Activation

Higher viral loads and increased immune activation in HIV-infected individuals can lead to altered iron metabolism. The virus's interaction with immune cells can stimulate inflammatory cytokines, enhancing hepcidin production and leading to reduced iron availability for erythropoiesis (red blood cell production)[77].

Antiretroviral Therapy (ART)

Different ART regimens can have varying impacts on iron metabolism. Some antiretroviral drugs may have direct or indirect effects on iron regulation. For instance:

- **NRTIs (Nucleoside Reverse Transcriptase Inhibitors)**: Some studies suggest that specific NRTIs may influence iron metabolism through effects on mitochondrial function, leading to altered iron handling.
- **Protease Inhibitors**: These agents can induce inflammatory responses, potentially affecting hepcidin levels.

Molecular Mechanisms

High iron levels typically increase hepcidin expression, while low iron levels decrease it. As mentioned earlier, cytokines like IL-6 can induce hepcidin production, affecting iron availability. Increased demand for erythropoiesis (e.g., due to anemia) can suppress hepcidin, enhancing iron absorption and release from stores. The expression of iron transport and storage proteins, such as transferrin receptor (TfR) and ferritin, can vary between individuals, impacting iron availability. Elevated TfR levels may indicate increased iron demand, while changes in ferritin levels can reflect iron stores and inflammation[78].

Outcomes and Implications

Individual variations in iron metabolism can lead to clinical outcomes such as anemia or iron overload. Anemia in HIV-infected individuals may stem from chronic inflammation, nutritional deficiencies, or ART side effects, while iron overload can occur in those with enhanced iron absorption or inadequate regulation. For example, individuals with high hepcidin levels may benefit from interventions aimed at reducing inflammation, while those with low hepcidin may need iron supplementation to support erythropoiesis. The integration of genetic, immunological, and nutritional assessments could lead to personalized approaches in managing iron metabolism in HIV-infected individuals. Tailoring ART regimens and dietary recommendations based on individual characteristics may improve clinical outcomes and quality of life[79].

Therapeutic strategies targeting iron metabolism

Addressing iron dysregulation in Human Immunodeficiency Virus (HIV) infection represents a promising therapeutic approach to mitigate disease progression and improve clinical outcomes. Iron chelators are compounds that bind to excess iron in the body, forming stable complexes that are excreted through urine or feces. Iron chelation therapy has been investigated as a potential therapeutic strategy to limit

iron availability and inhibit viral replication in HIV-infected individuals. Chelators such as deferoxamine and deferasirox have shown efficacy in reducing intracellular iron levels and suppressing HIV replication in preclinical studies. Clinical trials evaluating the safety and efficacy of iron chelation therapy in HIV-infected individuals are warranted to validate its potential as an adjunctive treatment modality[80]. Hepcidin, a key regulator of systemic iron homeostasis, plays a central role in iron metabolism and immune function. Modulating hepcidin expression or activity could restore iron homeostasis and mitigate HIV-associated complications. Hepcidin agonists, which mimic the action of endogenous hepcidin, may help suppress iron release from macrophages and hepatocytes, reducing iron availability for viral replication. Conversely, hepcidin antagonists could promote iron mobilization from cellular stores, limiting iron sequestration and enhancing immune function. Further research is needed to elucidate the therapeutic potential of hepcidin modulation in HIV infection. Given the role of oxidative stress in HIV pathogenesis, antioxidant therapy represents a complementary approach to target iron-induced oxidative damage. Antioxidants such as vitamin C, vitamin E, and glutathione may help mitigate oxidative stress by scavenging reactive oxygen species (ROS) and reducing lipid peroxidation. Additionally, antioxidant compounds with iron-chelating properties, such as green tea catechins and curcumin, could offer dual benefits by inhibiting viral replication and ameliorating oxidative stress-mediated tissue injury[81].Dietary interventions aimed at optimizing iron intake and absorption may help modulate iron metabolism in HIV-infected individuals. Iron-rich foods, such as lean meats, poultry, fish, legumes, and fortified cereals, can help replenish depleted iron stores and support immune function. Conversely, dietary strategies to limit iron absorption, such as avoiding iron supplements and reducing consumption of heme iron sources, may be beneficial in individuals with iron overload. Furthermore, supplementation with micronutrients, such as vitamin A, zinc, and selenium, which play roles in immune function and antioxidant defense, may complement therapeutic interventions targeting iron metabolism.

Therapeutic interventions of iron metabolism in HIV

Therapeutic interventions targeting iron metabolism in the context of HIV aim to address the complex interplay between iron dysregulation, immune activation, and disease progression. Modulating iron levels, influencing hepcidin regulation, and mitigating the impact of iron-mediated inflammation are potential strategies. Iron chelation involves the administration of agents that bind and remove excess iron from the body. By reducing iron availability, this approach aims to limit the co-factor function of iron for viral enzymes, potentially inhibiting HIV replication. Balancing the need for iron for normal cellular function against the potential adverse effects of iron deficiency requires careful consideration. Hepcidin upregulation in response to inflammation contributes to iron sequestration. Modulating hepcidin expression may help restore iron homeostasis. Chronic inflammation is associated with increased hepcidin production and alterations in iron metabolism. Anti-inflammatory agents may mitigate these effects. Ensuring adequate but not excessive iron intake is essential for supporting overall health and immune function. Effective ART can positively impact iron metabolism by reducing the chronic immune activation associated with active HIV replication. Recognizing the heterogeneity in iron metabolism among HIV-positive individuals and customizing treatments accordingly. Continuous monitoring helps adjust therapeutic interventions based on evolving patient needs and responses. Developing effective therapeutic interventions for iron metabolism in HIV requires a nuanced understanding of the dynamic interactions between the virus, host immune response, and iron homeostasis[81,82].

The development of new antiretroviral drugs: A narrative

Since the identification of HIV as the causative agent of AIDS in the early 1980s, the quest to develop effective treatments has evolved from a desperate struggle against a seemingly insurmountable epidemic to the emergence of sophisticated therapies that have transformed HIV from a fatal illness to a manageable chronic condition.

The early years: A desperate need for solutions

In the early days of the HIV/AIDS epidemic, the lack of effective treatments led to widespread fear and uncertainty. The first antiretroviral drug, AZT (zidovudine), was approved by the FDA in 1987, offering a glimmer of hope. However, its efficacy was limited, and the side effects were severe, leaving patients and clinicians yearning for better options. The discovery of the virus's replication mechanisms and the identification of its life cycle presented a pathway for drug development, spurring researchers to explore various therapeutic targets[80].

The rise of combination therapy

As the limitations of monotherapy became apparent, the concept of combination therapy emerged. The late 1990s marked a turning point in HIV treatment with the introduction of Highly Active Antiretroviral Therapy (HAART). This regimen, which combined multiple antiretroviral drugs from different classes, dramatically reduced viral loads and improved patient outcomes. The success of HAART demonstrated that targeting HIV from multiple angles could effectively suppress viral replication and prevent resistance, setting the stage for future drug development[81].

Innovations in drug classes

The quest for new antiretroviral agents led to the development of several classes of drugs, each targeting different stages of the viral life cycle:

1. **NRTIs (Nucleoside Reverse Transcriptase Inhibitors)**: Building on the initial success of AZT, researchers developed additional NRTIs, such as lamivudine, abacavir, and tenofovir, which offered improved efficacy and safety profiles.
2. **NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)**: Introduced in the

mid-1990s, NNRTIs, including efavirenz and nevirapine, provided an alternative mechanism to inhibit reverse transcription, further expanding treatment options.

3. **PIs (Protease Inhibitors)**: The development of PIs such as ritonavir and lopinavir revolutionized HIV treatment. These drugs inhibit viral protease, preventing the maturation of infectious viral particles.
4. **Entry Inhibitors**: As understanding of HIV entry mechanisms improved, drugs like maraviroc (a CCR5 antagonist) and enfuvirtide (a fusion inhibitor) were developed to block the virus from entering host cells.
5. **Integrase Strand Transfer Inhibitors** (INSTIs): The introduction of INSTIs, including raltegravir and later dolutegravir, represented a significant advancement in HIV therapy. These drugs inhibit the integrase enzyme, preventing viral DNA from integrating into the host genome, which is crucial for viral replication[81].

The era of long-acting formulations

The evolution of antiretroviral therapy took a groundbreaking turn with the introduction of long-acting formulations. Traditional daily regimens posed adherence challenges, particularly in populations with limited access to healthcare. Researchers sought to create injectable formulations that could sustain therapeutic drug levels over extended periods. In 2021, the approval of cabotegravir and rilpivirine as a long-acting injectable regimen marked a pivotal advancement. Administered every month or every two months, these therapies provided a promising solution for improving adherence and reducing the burden of daily pill regimens[82].

The role of global collaboration

The development of new antiretroviral drugs is a collaborative effort that spans continents and disciplines. Public-private partnerships, academic institutions, and non-profit organizations have come together to share knowledge, resources, and expertise. Initiatives like the Global Fund and PEPFAR have played critical roles in funding research, ensuring access to treatments, and supporting prevention efforts worldwide[82].

Future directions of iron metabolism in HIV

Exploring the future directions of iron metabolism in HIV involves addressing gaps in knowledge, leveraging emerging technologies, and developing innovative approaches to better understand and manage the intricate interplay between iron dynamics and HIV pathogenesis. Several potential avenues for future research and advancements in this field can be considered: Recognizing the heterogeneity of iron status among HIV-positive individuals and developing personalized therapeutic strategies to optimize outcomes. Utilizing advanced imaging technologies, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), to enhance our understanding of iron localization and its impact on specific tissues during HIV infection. Integrating genomics, transcriptomics, proteomics, and metabolomics to uncover the intricate networks governing iron homeostasis and its dysregulation in the context of HIV. Discovering novel biomarkers that reflect the nuanced changes in iron metabolism during different stages of HIV infection and treatment. Designing interventions that selectively modulate iron pathways involved in HIV replication without compromising essential cellular functions, providing more effective and targeted treatment options. Conducting comprehensive longitudinal studies to elucidate the relationship between iron dynamics, chronic inflammation, and the development of comorbidities such as cardiovascular diseases and neurocognitive disorders. Investigating how alterations in the gut microbiome, common in HIV, influence iron absorption, regulation, and utilization, potentially impacting systemic iron levels. Recognizing the global variation in nutritional and infectious disease profiles, studying iron metabolism in diverse populations to develop context-specific interventions. Investigating how co-infections, such as viral hepatitis or parasitic infections, interact with HIV and influence iron homeostasis, potentially exacerbating complications[80-82]. The future of research in iron metabolism and HIV involves a multidisciplinary approach, incorporating cutting-edge technologies, personalized medicine strategies, and a deeper understanding of the complex interactions shaping disease outcomes. Advances in these directions have the potential to refine therapeutic interventions and contribute to the development of more targeted and effective strategies for managing HIV and its associated complications.

CONCLUSIONS

Iron is essential in various physiological processes, such as oxygen transport, energy generation, and enzymatic activities. Ensuring efficient iron use and storage is crucial for overall health and wellness. A well-rounded diet high in iron-rich foods, combined with vitamin C sources to boost iron absorption, can assist in fulfilling daily iron needs. Consistent tracking of iron levels and proper handling of iron-related issues, like deficiency or excess, are crucial for avoiding negative health effects. Moreover, lifestyle elements like consistent exercise and donating blood can aid in maintaining healthy iron metabolism. Seeking advice from healthcare experts for tailored suggestions and direction on handling underlying issues impacting iron levels is essential. Implementing these strategies and staying alert to iron levels allows individuals to support ideal iron balance and minimize the likelihood of iron-related issues. Ultimately, preserving a careful equilibrium in iron use and storage is essential for promoting overall health and wellness. By focusing on diet, lifestyle choices, and medical care when needed, individuals can effectively handle the intricacies of iron metabolism and reap the rewards of lasting health.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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