

Review

## Role of P-selectin, hemopexin, lactoferrin, iron and ferritin in patients with giardiasis and amoebiasis: a narrative review

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**Abstract:** The most frequent intestinal parasites that cause severe disorders in humans are *Giardia lamblia* and *Entamoeba histolytica*, which alter serum concentrations of deferent markers due to virulence factors and pathogenicity. A large number of people with infection are asymptomatic, and they can go for up to a year without showing any signs or symptoms. Additionally, due to prolonged diarrhoea but not acute diarrhoea, these parasites can cause malnutrition, weight loss, growth delay, and possibly low cognitive development. The aim of this study is to look at how giardiasis and amoebiasis affect the levels of certain biomarkers in the blood.

**Keywords:** Lactoferrin, P-selectin, Giardiasis, Iron, Ferritin.

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### Introduction

*Entamoeba histolytica* (*E. histolytica*), a gastrointestinal protozoon, causes amoebiasis, which is spread by contaminated food and drink. The parasite does not always cause symptoms after it is introduced. A higher percentage of infected people are asymptomatic, and they can be asymptomatic for up to a year. Even after symptoms appear, the condition can be deadly because it can produce diarrhoea, which can lead to severe dehydration [1, 2, 3, 4]. The Galactose/N-acetylgalactosamine (Gal/GalNAc) lectin is ligated in phagocytosis [5], and amoeba spores and cysteine proteinases are released to the phagosome to enhance degradation [6].

*E. histolytica* requires a high quantity of iron to survive, and it can obtain iron from host proteins such haemoglobin, ferritin, Lactoferrin, and transferrin. That clathrin-coated pits in *E. histolytica* trophozoites endocytose ferritin, which is then destroyed in the endosome/lysosome pathway by particular cysteine proteases [7]. Ferritin is a heteropolymer made up of 24 subunits of two types, H and L, whose proportions are determined by the protein's principal function. In the liver and spleen, for example [8].

Giardiasis is a parasitic infection caused by the *Giardia lamblia* (*G. lamblia* parasite) that can be acute or persistent. Vitamin deficiencies, lactase insufficiency, fatty diarrhoea, gut cramping, irritable bowel syndrome, and weariness are all symptoms associated with chronic diseases [9, 10].

*G. lamblia* is a pathogenic protozoan that colonizes the small intestine of people and causes severe gastrointestinal sickness by attaching itself firmly to the host intestine [11, 12]. This parasitic organism is found throughout the world and can cause chronic diarrhoea and human malnutrition [11, 13]. The parasite's cyst can withstand improper conditions and adapt to the external environment to survive, but the trophozoite is in charge of virulence and clinical symptoms in the host [14].

According to Shepherd and Gibson (2006) [15], many pathological alterations occur in the small intestine of humans, leading in nutrient malabsorption, similar to non-infectious intestinal illnesses such as irritable bowel syndrome and celiac Crohn's disease. This disease also impacted iron levels, vitamin A levels, and cognitive development [16, 17].

The virulence of the *Giardia* strain, the number of developed cysts eaten, the age of the individual, and the host's immune system all play a role in the clinical symptoms of giardiasis [18]. Several studies have linked human giardiasis to nutrient malabsorption and micronutrient deficiencies such as zinc, vitamin B-12, vitamin A, and iron [19, 20, 21].

The presented review aims to overview the evaluation of human serum levels of p-selectin, Hemopexin, Lactoferrin, Iron and Ferritin in patients with giardiasis and amoebiasis disease. In order to shed light on the relationship between infection with intestinal parasites and its relationship to inflammation and anemia resulting from infection with these intestinal parasites such as *E. histolytica* and *G. lamblia*.

### P-selectin

P-selectin is a cell adhesion protein found on epithelial cells and platelets and belongs to the selectin family. It was initially discovered in an endothelial cell in 1989 [22]. Through proteolytic cleavage of membrane-bound p-selectin, activated epithelial cells and activated platelets secrete the soluble form of P-selectin [23]. The SELP gene encodes P-selectin in humans [24]. L-selectin, whose expression is restricted to leukocytes and linked to leukocyte adhesion to vascular endothelial cells, is one of three members of the selectin family. [25], Express E-selectin, and the last one is P-selectin which is mentioned previously. All these selectins are derived from duplication of a single gene and are involved in early adhesive interactions between leukocytes, platelet and endothelial cells [26]. In humans, P-selectin has 17 exons and is found on chromosome 1q21-q24, which spans more than 50 Kb [27]. P-selectin is anchored in the transmembrane region, followed by the brief part of the cytoplasm [28]. P-self-limited selectin's surface expression allows it to mediate leukocyte anchoring to the vessel wall during the early stages of acute inflammation [29, 30, 31].

The P-selectin sorted in the trans-Golgi network has a relatively extended half-life after synthesis for transport to secretory granules [31]. Not sorted protein is swiftly absorbed in Catherin-coated pits and transported to the plasma membrane [32]. After being stimulated by inflammatory mediators such as tumor necrosis factor and interleukins, P-selectin translocated from its storage organelles to the cell surface within minutes, binding to T-cells, resulting in the expression of functional P-selectin ligands and initiating the early step of recruitment of leukocytes into inflammation sites [33,34,35]. The primary role of P-selectin in response to inflammation is leukocytes recruitment to sites of inflammation by mediating enhanced leukocytes tethering and slow rolling but in state of ineffective engagement of selectin resulted in reduced leukocytes tethering and increased rolling velocities on regular endothelial so that lead to impaired leukocytes recruitment to sites of inflammation [36]. One trigger that stimulates endothelial cells to release P-selectin is thrombin. According to some studies, the calcium ions-independent pathway is involved in releasing P-selectin [37]; also, P-selectin and E-selectin are induced by TNF- $\alpha$  to express them on intestinal endothelial cells *vitro* and *in vivo*. And from *in vitro* data, IL-4 stimulate human umbilical endothelial cells, human intestinal endothelial cells and porcine aortic endothelial cell to express the p-selectin [38, 39].

Although the effects of IL-4 on mouse ECs are delayed compared to TNF-, both works to promote p-selectin expression in mice and humans. In tissues with chronic or allergic inflammation, such as rheumatoid synovium atherosclerotic plaque, P-selectin is also persistent on the surface of endothelial cells [32]. In nasal polyposis was observed that IL-4 could induce prolonged expression of p-selectin in human umbilical vein endothelial cells [40, 41]. P-selectin levels were noted in some parasitic infections [23]. Exposure to oxygen radicals also induces prolonged expression of p-selectin on the cell surface, mediating neutrophils under static conditions [41]. As determined by flow cytometric bind to p-selectin IgM fusion protein in polarized T-cells isolated from lymphoid tissues, Th1 and Th2 lymphocytes exhibited equal quantities of selectin ligand [42, 43, 44].

### Lactoferrin

Lactoferrin is an iron-binding glycoprotein; It is one of the families of transferrin, which is almost 300-500 million years old [45]. It is a protein composed of single-chain about 690 amino acids and 77kDa molecular weight [46]. Lactoferrin is more stable and rigid without iron (apo Lactoferrin). Despite this, it has a high isoelectric point (pI Lactoferrin). It may connect several cells when charged with iron (holo Lactoferrin), indicating that it has a biological role as an antibacterial, antitumoral, and antioxidant agent [45, 47, 48, 49].

Exocrine glands produce Lactoferrin in the digestive and respiratory tracts [50, 51]. Lactoferrin can also be found in milk, saliva, tears, sperm, and colostrum. Furthermore, (apo Lactoferrin) acts as an acute-phase protein to release infection in the injection site and stop the pathogens requiring iron for growth. The granules of neutrophils and neutrophils can remove this; LF is an efficient iron scavenger because it is mainly unsaturated (up to 86%) [52, 53, 54, 55, 56]. Lactoferricin (LFcin) result from the digestion of bovine Lactoferrin, which has additional effectiveness versus pathogen better than native protein [57, 58]. Else have activity as bactericidal, and candidacidal was discovered is LF peptide called LF-ampin [59, 60, 61].

Protozoan infection can lead to intestinal amoebiasis to cause diarrhoea in children, and 4th cause of death in the world. E. histolytica must use complicated methods to infiltrate the gut mucosa. [62, 63].

Apo-LF is a protein of milk with super effect as amoebicidal *in vitro* so that the parasite can damage by membrane disruption. In contrast, Lactoferrin can bind the lipids of the membrane of the cell [63]. LF has several functions; therefore, it is regarded as a critical component in the first line of host defence because it can respond to physiological and environmental conditions [64]. In addition to their role in Fe<sup>3+</sup> homeostasis, lactoferrin structural characteristics make them useful as antimicrobials against bacteria, fungi, yeasts, viruses, and parasites [65], anticarcinogenic, anti-inflammatory, and different enzymatic functions [64, 66].

Several studies have shown that Lactoferrin plays an essential role in the hemostasis of the body's iron level, particularly in milk; as a result, there are no iron deficiencies in infants who are breastfed. On the other hand, those fed Lactoferrin-free milk appear to have iron deficiency and other diseases [67, 68].

Lactoferrin can affect both acquired and innate immune systems, so when a pathogen penetrates tissue, innate immune cells produce pro-inflammatory cytokines. Lactoferrin affects both the innate and acquired immune systems in this way. The innate immune system releases cells after a microorganism penetrates a tissue, increasing blood vessel permeability and preparing neutrophils to proceed to the infection site [69]. Whereas increased local concentrations of Lactoferrin released from neutrophil granules can interact with cells of both immune systems to regulate proliferation and differentiation. [69,70]. Lactoferrin from both humans and cattle can eradicate amoeba in a concentration-dependent way. On the other hand, antimicrobial action can be inhibited by Fe<sup>2+</sup> – Fe<sup>3+</sup> or other divalent cations such as Mg<sup>2+</sup> and Ca<sup>2+</sup> [71, 72].

### Hemopexin

Hemopexin is a plasma protein-bound heme released extracellularly from Hb and another plasma protein; iron homeostasis relies on Hb heme removal, limiting. Many parasitic pathogens, including Trypanosoma, Leishmania and Entamoeba, have advanced convergent techniques of (heme-iron) gaining from this molecule of the host. Heme-iron is released by digested a protein portion of hemoglobin after pathogen protozoa are captured through the specific surface receptors or phagocytosis [72, 73, 74].

Hemopexin, also known as beta-1B-glycoprotein, is a 60-kDa acute-phase protein with the highest affinity for heme of any protein type [75]. Thus, HPX binding to heme can prevent free heme from intercalating into cell membranes and other lipophilic structures, such as Low-Density Lipoprotein (LDL), which has oxidant and pro-inflammatory properties [76, 77].

HPX is mainly expressed in the liver, with little expression in the central nervous system's neurons and astrocytes, the retina's ganglionic and photoreceptor cells, the peripheral nervous system's Schwann and fibroblast-like cells, kidney mesangial cells, and skeletal muscle [78, 79].

Appear as the first line of defence versus toxicity of heme because of its ability to link heme with the highest affinity and to function as a distinctive heme carrier to the liver [78], to demonstrated and promote the delivery of heme to the liver; parenchymal cells must form the formation of the complex between heme and HPX [80]. Its job is to protect the organism from oxidative damage caused by free heme by scavenging heme released or lost during the turnover of heme proteins like hemoglobin. HPX's heme scavenging ability is especially useful in decreasing scheme toxicity in vascular endothelium [79]. When heme binds to albumin, it can quickly enter endothelial cells; this process can be stopped in the presence of hemopexin; heme seizure within the Hemopexin complex also ensures protection against oxidation processes in extracellular space and prevents scheme triggering. [81]. In vivo, the hemopexin complex is mainly cleared via receptor-mediated endocytosis of hepatocytes [82]. When hemopexin reacts with the receptor of liver cells, it releases a bound ligand for intromission so that this process can preserve the iron of the body [83].

As a prosthetic group attached to diverse proteins, the tiny molecule heme performs essential tasks such as oxygen binding, electron transport, catalysis, and intracellular signalling. On the other hand, free heme is a powerful oxidant that causes cytotoxicity and inflammation [83]. Circulating heme produced from proteins after cell breakdown has been associated with various diseases, including atherosclerosis, renal injury, and CNS damage [84]. Because erythrocyte hemoglobin contains a large amount of heme, it is essential in treating acute and chronic bleeding and hemolysis.

Respectively, haptoglobin and hemopexin bind to hemoglobin and heme, limiting their reactivities and allowing receptor-mediated endocytosis to degrade them. Kristiansen and et al. (2001) [85] recognized the monocyte and macrophage protein CD163 as a scavenger receptor for hemoglobin-haptoglobin. Low-density lipoprotein (LDL) was shown to remove hemopexin-heme from circulation by low-density lipoprotein receptor-related protein (LRP/CD91), a multifunctional scavenger found in the brain, placenta, liver, macrophages, and monocytes by the same group [85]. Together, an essential set of pathways that protect

against noxious free heme and identify new areas of investigation for heme biology these studies define. Under its restricted expression pattern, hemopexin-heme is delivering into specific tissues by LRP/CD91. It has potential biological consequences. In lysosomes, hemopexin is degraded where LRP/CD91 transports its cargo, presumably releasing intact heme. Inside cells, by modulating the DNA binding activity and subcellular localization of transcription factors, heme regulates gene expression [86]. One consequence is that heme degrades metabolites with potent antioxidant and anti-inflammatory activities of heme oxygenase-1 (HO-1)[87]. A recent study found that in monocytes, hemopexin-heme taken up by LRP/CD91 induces HO-1, which might inhibit their inflammatory function. Heme recruitment could cause HO-1 and its beneficial effects in other tissues as well by LRP/CD91. The chronic neurodegenerative disorders and acute tissue damage after intracranial hemorrhage CNS are interesting because free heme is implicated in this pathogenesis [83].

Moreover, in cerebrospinal fluid, hemopexin is abundant LRP/CD91 is expressed in neurons. When heme is transported into cells by LRP/CD91 could remain intact and be recycled directly into proteins, for example, in hepatocytes, where LRP is expressed. Although protein heme requirements are relatively high, neurons might protect by stimulating heme absorption by LRP/CD91 by activating HO-1. Plasma protein scavenging, intracellular signalling, and neurotransmission are all functions of LRP/CD91, a transmembrane protein. These roles may alter Hemopexin-heme binding, especially in pathological situations where the receptor is saturated [83, 84]. For example, in blood coagulation, plasma proteases are removed by LRP/CD91 and cofactors involved. High levels of hemopexin-heme may modulate LRP function influence this process to impact clot formation or dissolution. In principle, this mechanism associated with many hemolytic disorders could contribute to thrombophilia [88].

Finally, genetic differences in heme uptake pathways may play a role in prevalent multifactorial disorders. Polymorphisms in Haptoglobin, for example, affect vascular problems in diabetics, owing to functional variations in neutralizing the oxidative effects of globin-associated heme. It is also possible that in heme metabolism, genetic variations by the newly defined hemopexin-heme-LRP/CD91 pathway affect susceptibility to vascular and nervous system disorders that are perpetuated by oxidative injury.

### Iron

Iron is an essential trace element for life and is found in practically all living species [89]. It is an enzyme cofactor that participates in oxygen and an accessible form of iron redox biological activities. On the other hand, the Fenton reaction produces reactive oxygen species, which can harm a variety of cell components. As a result, no free iron can be found [90].

Iron is essential for humans because it's used to transport oxygen to all cells in the body. The human body regulates iron absorption from the intestine lumen and acts to recycling it for use again. Still, the body has no specific mechanism for excreting iron and in patients with iron overload disorders, and iron toxicity starts over the ability of the body to bind and store it [91]. The iron is stored in liver cells, spleen and bone marrow bounding by ferritin [89]. The iron source binds to hemoglobin receptors [92].

When the body's iron stores are exhausted, a reduced supply of iron to multiple tissues manifests as iron insufficiency. It is the most common nutrient deficiency [93]. The leading cause is low

absorption of bioavailable iron from the diet, rapid growth, and iron spoilage due to small intestines' imperfect absorption of food materials. [94]. One possible cause of anemia is the infection with intestinal parasites available only from small, unrepresentative sample surveys [95].

Reduced intestinal surface area and microvilli distortion are two of the many causes of malabsorption in giardiasis, impairing iron absorption because this is the primary location for iron absorption. [96, 97]. Giardiasis is a parasitic infection caused by *G. lamblia* that causes poor iron absorption in the intestine and low serum iron levels [98].

### Ferritin

Apo-ferritin is ferritin without the associated iron. It is made up of 24 polypeptide chains with two subunits (heavy and light subunits). The L subunit is in charge of long-term iron accumulation in the liver and spleen [97, 98]. In contrast, the H subunit is involved in iron transport [99]. The ratio of H to L subunits in ferritin varies greatly depending on the tissue type and physiologic status of the cells, ranging from mostly L in the liver and spleen to predominantly H in the heart and kidney. The ratio isn't set in stone, but it is rather malleable. It is an immune-inflammatory and infectious condition that has been transformed [100, 101].

Ferritin's role in macrophages is the most crucial function in humans. It transports iron from older blood cells to Apo ferritin, which it recycles. The cycle is completed when the iron in the transferrin is transferred to immature red blood cells in the bone marrow. Iron homeostasis and intracellular labile iron storage are ferritin's significant functions. [101]. Ferritin plays an important part in the host's immunological response, as indicated by its increased concentration during infection to combat infective pathogens attempting to bind iron from the host tissue [102]. Although ferritin levels in human serum are low, they are raised in iron overload and inflammation [100, 103]. Because serum ferritin and iron respond to inflammation in an acute phase, total iron and ferritin levels can rise independently of marrow iron reserves and ferritin levels [104].

The ferritin calculation helps evaluate iron metabolism, and analysis at the beginning of therapy measures the body iron reserves. It can detect a lack of storage in the reticuloendothelial system in a very early stage [105]. The ferritin concentration is high at birth, rising during the first two months of life and then fall throughout later infancy [106, 107, 108, 109]. These biomarkers such as p-selectin, Hemopexin, Lactoferrin, Iron and Ferritin correlated with intestinal parasites infection and this study of biomarkers such as p-selectin, Hemopexin, Lactoferrin, Iron and Ferritin correlated with intestinal parasites infection and this study considered as the essential study for anthers studies in the relationship between these biomarkers and iron deficiency anaemia in human infected with intestinal parasites.

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### Conclusion

The present study concluded that the giardiasis and amoebiasis disease caused decreased serum levels of p-selectin, Hemopexin, Lactoferrin, Iron and Ferritin.

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### Conflict of interest

There are no conflicts of interest stated by the authors.

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