INTRODUCTION

Iron deficiency is defined as decreased total body iron content ***(Cardenas et al., 2006).*** It is the most common cause of anemia in both underdeveloped and developed nations and the most organic disorder in clinical practice ***(Dubois and Kearney, 2005).***

Iron deficiency anemia (IDA) results in impairments in immune, cognitive, and reproductive functions, as well as decreased work performance ***(Cardenas et al., 2006).***

The onset of IDA is usually insidious, and the progression of symptoms is gradual ***(Andrwes, 2009).***

In IDA, the erythrocytes are hypochromic and microcytic, the plasma iron concentration is diminished, the iron binding capacity increased and the serum ferritin concentration is low ***(Beutler, 2007).***

IDA may occur as a result of chronic blood loss, inadequate dietary iron intake, malabsorption of iron, diversion of iron to fetal and infant erythropoiesis during pregnancy and lactation, or a combination of these factors. In men and in postmenopausal women, iron deficiency is most commonly caused by chronic bleeding from the gastrointestinal tract as peptic ulcer, hiatal hernia, gastritis, hemorrhoids, vascular anomalies, and neoplasms ***(Beutler, 2007).***

The failure to identify a cause of iron deficiency in some patients with low iron stores raises the question of whether there are additional unexplained causes of iron depletion. Some authors suggest a relationship between Helicobacter pylori gastritis and IDA in the absence of peptic ulcer disease ***(Dubois and Kearney, 2005).***

Helicobacter pylori is a micro-aerophilic, Gram-negative, spiral shaped and flagellated organism. It is the most common chronic bacterial infection of humans and present in almost half of the world population ***(Frenck and Clemens, 2003).***

Helicobacter Pylori infection can induce asymptomatic gastritis, peptic ulcer disease and gastric carcinoma ***(Kato and Sherman, 2005).***

Diagnosis of Helicobacter pylori can be made with both invasive and noninvasive tests. Invasive tests include histology, culture, and rapid urease test which require endoscopy to obtain biopsies of the gastric mucosa. Noninvasive tests for the diagnosis of Helicobacter pylori are based on analysis of samples of breath, blood, or stool ***(Zakaria and Ahmed, 2009).***

AIM OF THE WORK

The aim of this work was to study the association between unexplained iron deficiency anemia and Helicobacter pylori infection and to assess the association between the severity of iron deficiency anemia and Helicobacter pylori infection.

NORMAL IRON METABOLISM

Introduction

Iron is one of the most widely spread metals in the earth's crest ***(Atanassova and Tzatchev, 2007).*** Iron is essential for almost all forms of life and its biological role is attributable to its properties as a transition metal. It readily switches between its ferric (3+) and ferrous (2+) state and therefore serves as an essential prosthetic group in most cellular electron-transfer reactions ***(Lopes et al., 2010).***

Iron is a critical component of heme in hemoglobin and myoglobin, where it serves in oxygen binding and transport ***(Lopes et al., 2010).*** However excess of iron is highly toxic because of its ability to promote free radical formation ***(Atanassova and Tzatchev, 2007).***

In normal individuals, iron homeostasis is meticulously regulated to avoid deleterious extremes of iron deficiency and iron overload ***(Andrews, 2009).***

(A) Importance of iron in our life:

Iron is an essential micronutrient, as it is required for adequate erythropoietic function, oxidative metabolism and cellular immune responses ***(Munoz et al., 2009).***

Iron makes up the central core of the hemoglobin molecule, a protein that gives color to red blood cells and transports oxygen

in the blood. Iron is also necessary for collagen synthesis and oxidation of fatty acids. It is also a cofactor in neurotransmitter synthesis for serotonin, dopamine and noradrenalin, which modulate mood and behavior ***(Lopes et al., 2010).***

Hundreds of enzymes have iron as a constituent or need it as a cofactor in reactions. One of iron's best known roles is a component of enzymes involved in energy metabolism. Cytochromes, for example, are heme-containing compounds critical to the electron transport chain. Iron also is a cofactor for antioxidant enzymes that protect against damaging free radicals. It is also essential for optimal brain and nervous system development and function. It has a role in myelinatization (the development of myeline sheath around nerve fibres). Also, optimal immune function requires iron ***(Insel et al., 2010).***

(B) Sources of Iron in food:

Dietary iron is found in two basic forms, either as heme found in meat and meat products (derived from the hemeoglobin, myoglobin, and other heme proteins in foods of animal origin) or non-heme iron-present in cereals, vegetables, beans, fruits ***(Darshan and Anderson, 2007).***

(C) Total body iron:

Iron content varies with age and sex. Full-term infants begin life with approximately 75 mg/kg body weight of iron,

mainly acquired from their mothers during the third trimester of gestation. These abundant stores are rapidly depleted over the first few months of life, and most young children are in a state of iron imbalance, as their intake must keep pace with rapid growth. Requirements decrease after adolescence, and men have a small, gradual increase in iron stores throughout life. The body iron content of normal adult men is 50 mg/kg body weight or greater. In contrast, post pubertal women have continuous loss of iron until they cease to menstruate, resulting in a body iron content averaging 35 mg/kg. After menopause, women accumulate iron linearly in parallel with adult men ***(Andrews, 2009).***

(D) Requirements of iron:

Table (1) shows daily requirements that are age and sex specific ***(Beutler, 2007).*** Requirements are higher in menstruating women and during periods of rapid growth in infancy and adolescence. Requirements are highest of all in pregnancy ***(Hoffbrand et al., 2011).***

Table (1): The minimal daily iron requirements:

	Amount that must be absorbed daily for hemoglobin synthesis (mg)	Minimal amount that should be ingested daily (mg)
• Infants	1	10
• Children	0.5	5
• Young non pregnant women	2	20
• Pregnant women	3	30
• Men and postmenopausal women	1	10

(Beutler, 2007)

(E) Distribution of body iron:

The concentration of iron in the adult human body is normally about 50mg/kg in males and 40 mg/kg in females ***(Hoffbrand et al., 2011).***

Most of the iron in the body is distributed within RBC hemoglobin (65%; 2300 mg/dl) (Figure 1). Approximately 10% is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes) (350 mg). The remaining body iron is stored in the liver (200 mg), macrophages of the reticuloendothelial system (RES; 500 mg), and bone marrow (150 mg) ***(Munoz et al., 2009).***

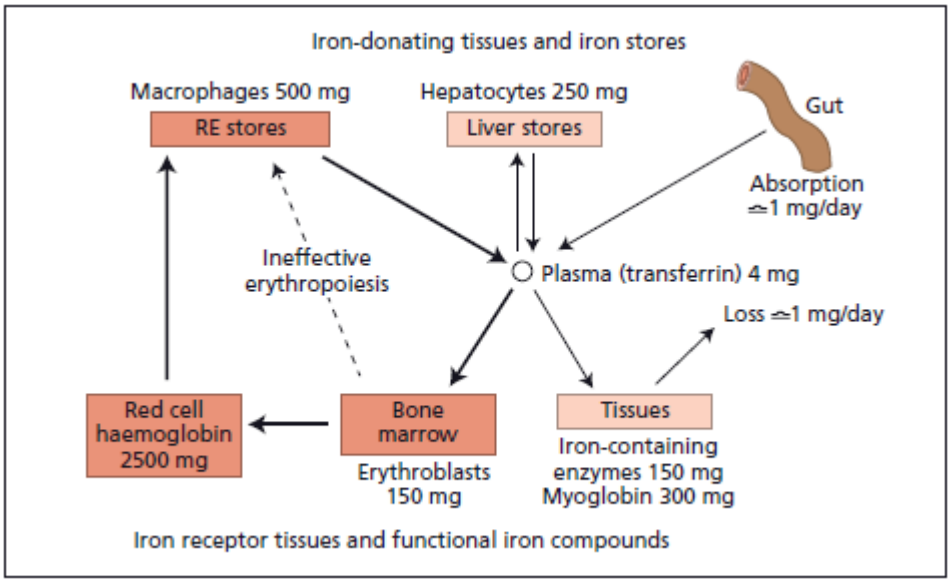

Figure (1): Distribution of iron in the body: RE: reticuloendothelial ***(Hoffbrand et al., 2011).***

(F) Iron compartments in humans:

Most of the body iron is found in heme compounds, including hemoglobin, myoglobin, and cytochromes (table2).Very small amounts are incorporated into enzymes that use iron in electron transfer, including peroxidases, catalases, and ribonucleotide reductase. Some is used in enzymes containing iron–sulfur clusters. However, most nonheme iron (approximately 1 g in adult men) is stored as ferritin or hemosiderin in macrophages and hepatocytes. Only a tiny fraction (~0.1%) is in transit in the plasma, bound to the carrier protein, transferrin ***(Andrews, 2009).***

Table (2): Iron compartments in human:

Protein	Function	Amount (g)	Percent of total
Hemoglobin	Erythrocyte oxygen transport	2.600	65.0
Myoglobin	Muscle oxygen storage	0.130	6.0
Transferrin	Plasma Fe transport	0.003	0.1
Ferritin	Intracellular Fe storage	0.520	13.0
Hemosiderin	Intracellular Fe storage	0.480	12.0
Catalase,Peroxidase	H_2O_2 degradation	—	—
Cytochromes	Electron transport	—	—
Aconitase	Tricarboxylic acid cycle	—	—
Ferrochelatase	Heme biosynthesis	—	—
Duodenal cytochrome b-like protein	Intestinal Fe reduction	—	—

(Andrews, 2009)

(G) Absorption of iron:

Iron absorption is defined as the physiological movement of iron into the enterocytes that line the luminal surface of the gastrointestinal tract and then into the bloodstream ***(Hunt, 2005).***

Nearly all absorption of dietary iron occurs in the duodenum. Several steps are involved, including the reduction of iron to a ferrous state, apical uptake, intracellular storage or transcellular trafficking, and basolateral release ***(Munoz et al., 2009).***

Iron transport across the intestinal epithelium is shown in (Figure 2)

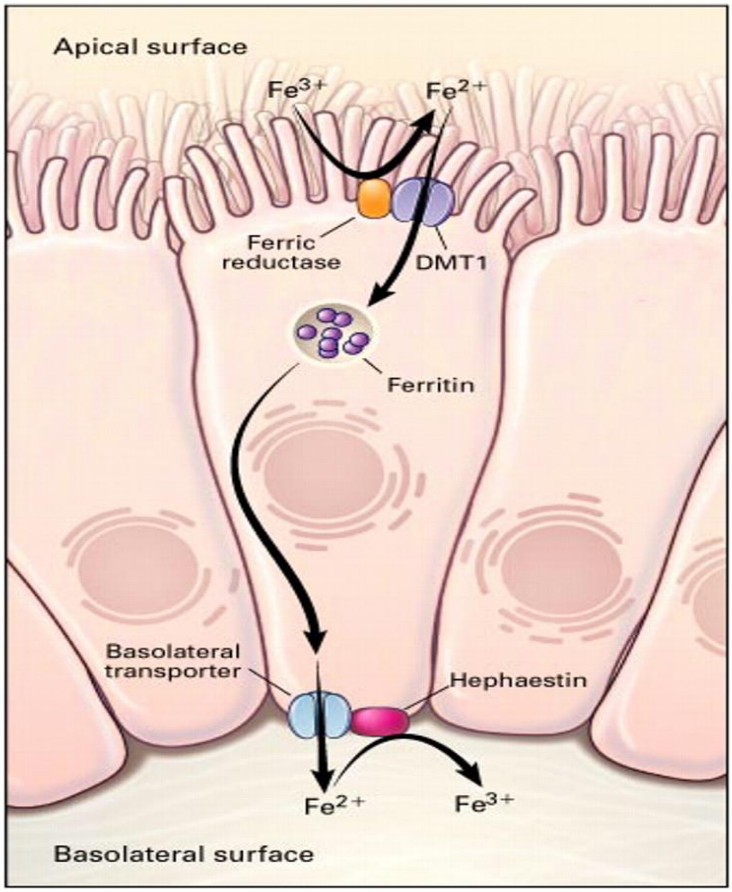

Figure (2): Iron Transport across the Intestinal Epithelium: Fe^{3+}: ferric, Fe^{2+}: ferrous, DMT1: divalent metal transporter 1 ***(Andrews, 2000).***

a) Iron reduction and apical uptake

There are two distinct pathways for iron uptake: one for uptake of heme iron and another for ferrous (Fe^{2+}) iron (non-heme) (Figure 3) ***(Andrews, 2005).***

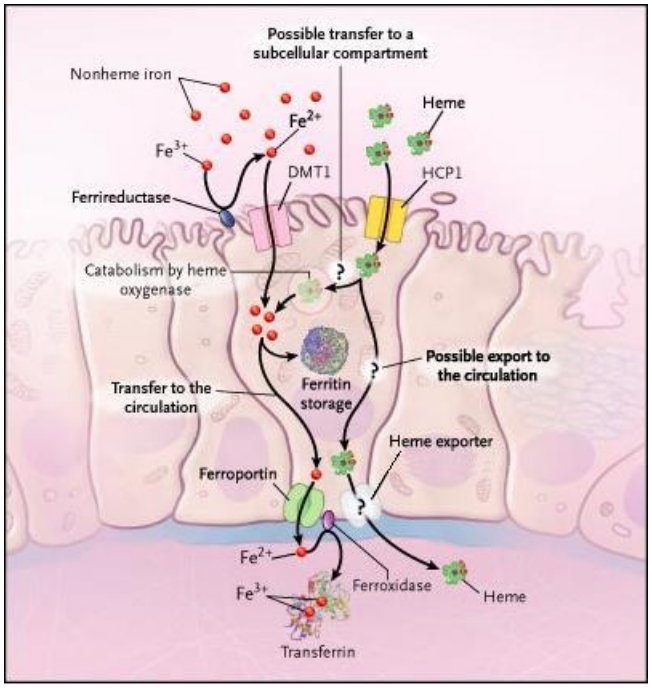

Figure (3): Heme and non-heme iron absorption pathways: Fe^{3+}: ferric, Fe^{2+}: ferrous, DMT1: divalent metal transporter 1, HCP1: heme carrier protein 1which brings heme into cells) ***(Andrews, 2000).***

Dietary non-heme iron primarily exists in an oxidized (Fe3+) form that is not bioavailable, and must first be reduced to the Fe2+ form by a ferrireductase enzyme, before it is transported across the intestinal epithelium by a transporter called divalent metal transporter 1 (DMT-1) ***(Munoz et al., 2009).***

Heme iron is absorbed into enterocytes by a heme carrier protein 1, which is a membrane protein found in the proximal intestine, where heme absorption is greatest. Once internalized in the enterocytes, it is likely that most dietary heme iron is released as ferrous iron by heme oxygenase to enter a common pathway with dietary non-heme iron before it leaves the enterocytes ***(Munoz et al., 2009).***

b) Fate of uptake iron

Iron taken up into the enterocyte may be further transported to the blood through the basolateral membrane, completing absorption, or it may be held and returned to the intestinal lumen with cellular desquamation ***(Hunt, 2005).***

The efflux of iron across the basolateral membrane and into the circulation is mediated by the iron transport protein ferroportin 1 ***(Frazer and Anderson, 2005).***

Ferrous iron once exported across the basal membrane by ferroportin 1, is then oxidized by a multi-copper oxidase protein called **hephaestin** (an enzymatic protein similar to plasma ceruloplasmin) before being bound by plasma transferrin ***(Munoz et al., 2009).***

- **Bioavailability**

The bioavailability of iron is influenced by a number of variables, e.g. the iron content of foods, the type of iron present, i.e. heme or non-heme, and other dietary constituents ***(Darshan and Anderson, 2007).***

Heme is the most bioavailable source of iron amounting to 20%-30% as it is well absorbed and unaffected by dietary composition and gastric acidity**.** In contrast, the bioavailability of non-heme iron is low, only 1%-10% of the dietary load is absorbed-and is strongly influenced by gastric acidity and other dietary components that can enhance or inhibit non-heme iron bioavailability ***(Andrews, 2009).***

Ascorbate and animal tissues are major dietary enhancers of inorganic iron absorption. Beef, lamb, pork, chicken, and fish considerably enhance non-heme iron absorption. Peptides containing cysteine have been shown to enhance non-heme iron absorption. Other possible enhancers of non-heme iron absorption include certain keto sugars, organic acids, and amino acids that form soluble iron chelates ***(Andrews, 2009).***

Other ingredients in foods can significantly inhibit non-heme iron absorption. Phytates, present in grains and some other vegetable foods, form stable, poorly absorbable complexes with iron. Bran and other fibers inhibit iron absorption mainly because of their phytate content. Polyphenols present in legumes, tea, coffee, and wine also interfere with iron absorption. Phosphates and phosphoproteins inhibit absorption of iron from egg yolks and milk. Calcium inhibits intestinal iron absorption and other metals, such as zinc and manganese, can compete for iron uptake ***(Andrews, 2009).***

Factors affecting iron absorption:

Table (3): Lists the factors affecting iron absorption.

Favoured by	Reduced by
a) Dietary factors: -Increased haem iron. -Increased animal foods. -Ferrous iron salts.	 -Decreased haem iron. -Decreased animal foods. -Ferric iron salts.
b) Luminal factors: -Acidic pH (e.g. gastric HCL). -Low-molecular-weight soluble chelates (e.g.vitamin C,sugars,amino acids). -Ligand in meat.	 -Alkalis (e.g.pancreatic secretions). -Insoluble iron complexes(phytates , tannates in tea ,bran)
c) Systemic factors: -Iron deficiency. -Increased erythropoiesis (e.g.after haemorrhage). -Ineffective erythropoiesis. -Pregnancy. -Hypoxia.	 -Iron overload. -Decreased erythropoiesis. -Inflammatory disorders.

(Worwood and Hoffbrand, 2005).

- **Regulation of intestinal iron absorption:**

Because the total body iron content is largely determined by the efficiency of absorption of iron, the regulation of absorption has been of great interest for many years. Two factors are of prime importance in determining absorptive rate. The first is the amount of storage iron in the body. When storage iron is depleted, iron absorption is increased; when it is excessive, iron absorption is decreased. This has been termed the stores regulator ***(Andrews, 2009).***

The second important factor is the overall rate of erythropoiesis and whether it is effective or ineffective. This erythroid regulator mediates an increase in intestinal iron absorption when the red cell production rate is increased. If iron is limiting, or in conditions with ineffective erythropoiesis, as seen in thalassemia syndromes, congenital dyserythropoietic anemias, and sideroblastic anemias iron absorption is decreased ***(Beutler, 2007).***

Two models have been proposed to explain how the absorption of iron is regulated. These models have been termed: (Figure 4)

1- The crypt programming model.

2- The hepcidin model.

1- **The crypt programming mode:** It proposes that enterocytes in the crypts of the duodenum take up iron from the plasma. The intracellular iron level of the crypt cells corresponds to the body's iron stores, which in turn determines the amount of iron absorbed from the gut lumen as these crypt cells migrate upwards to become absorptive cells at the brush border. The crypt cells express both transferrin receptor1 **(**Tfr1) and transferrin receptor2 (Tfr2) which mediate the cellular uptake of transferrin-bound iron from plasma ***(Munoz et al., 2009).***

2- **The hepcidin model:** Hepcidin is a small peptide hormone of 20 to 25 amino acids, which is cleaved from a larger