THE VALUE AND PRICE OF MEN'S ADDICTION TO IRON

On chronic iron deficiency and novel treatments relevant to corona days

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Despite major advances in Biology and Medicine and the increasing awareness of nutrition to human health and wellness, anemia remains a major public health problem. About half of the millions of anemia cases worldwide are associated with iron deficiency (ID) that manifest initially as physical fatigue and progressively leads to major dysfunctions with serious clinical outcomes. A major source of the problem is inadequate (ineffective or insufficient) food sources, that exacerbates during worldwide crisis, as in the present corona pandemics. Those affected are primarily children, young girls, pregnant women and the elder population. But among those most afflicted are individuals with chronic inflammatory disorders, as found in inflammatory bowel disorders IBD (Crohn's, ulcerative colitis, etc), in celiac, rheumatoid arthritis, most types of cancer and especially in infections (bacterial, viral or parasitic). How does one clinically cope with chronic ID in normal times and most importantly during periods of crisis, when clinical services relevant to the ID population are limited or inaccessible?

Where and how is the essential role of iron manifested in life?

The best known need for iron is in respiration and the most commonly known indicator is hemoglobin, whose role in blood is the capture of oxygen as red blood cells pass through capillaries in the lung and transfer it to all tissues. More than 75% of body iron is associated with the protein hemoglobin, 5% with muscle myoglobin, 15% with the liver and spleen (primarily stored in ferritin molecules) and only 5% in the rest tissues, mostly as heme and iron-sulfur proteins. These proteins confer to the iron a wide spectrum of chemical activities that are expressed in about 30% of all cell functions, such as: cell respiration, oxygen sensing, synthesis of DNA bases, of lipids, neurotransmitters in the excitable tissues in the brain and heart, etc. Among the vital iron-based functions we identify many that have been preserved throughout millions of years of evolution, most likely from life's onset in the anaerobic planet. However, with the advent of atmospheric oxygen, the available iron oxidized and precipitated as insoluble oxides, posing living systems with the major challenge of acquisition of the life-essential metal. The same challenge is faced by all higher organisms that for their survival in an aerobic world, they need to extract the metal from nutritional sources, absorb it and handle it cautiously by unique means. That is because ionic iron is catalytically active and in the presence of oxygen it is capable of generating noxious reactive oxygen species (ROS) that can damage cell components. The dual character of iron, essential but risky, pose all living cells with the double challenge of controlling the iron levels so as to meet cells metabolic demands and concurrently protecting cell components from potential hazardous iron-driven ROS formation. Although key players in cell antioxidant defense are cell enzymes that counteract ROS

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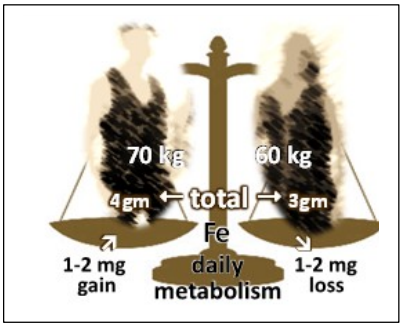
formation, it is the iron binding protein ferritin that plays an iron homeostatic role in cells by sequestering labile iron ions and retaining them intra-molecularly in chemically stable forms.

The dual nature of iron (life precious despite its limited availability and costly maintenance due to potential toxicity) has often led to the conundrum of evolution adhering to a life essential but quite risky component. The answer is apparently found in the dialectic question itself, iron might be life optimal though not ideal, addictive but also priceless and most likely too pricy to be replaced .

How does the daily human economy look like?



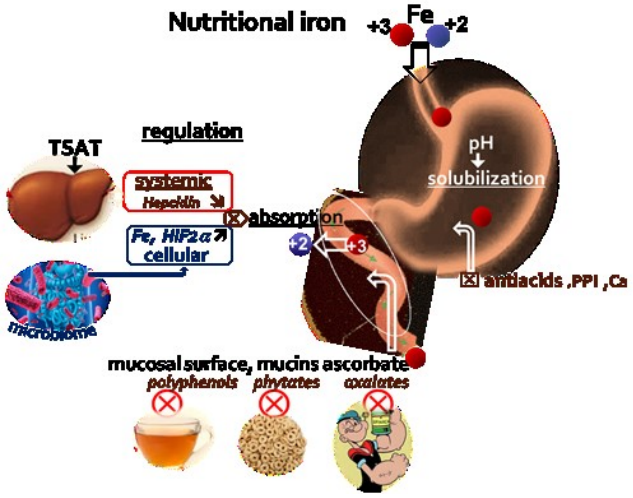
In normal individuals the body iron levels are maintained at steady state in the 3-4 gm range throughout adult life, based on a daily absorption of 1-2 mg that compensates for a commensurate loss of sloughed (mostly dead) cells from the skin and gut. The physiological balancing mechanism leans on a regulated absorption in the gut that responds to the levels of iron in the plasma. In the absence of an iron excretory path, any excess iron absorbed is diverted to the liver for storage, mostly in ferritin molecules. We can therefore view the iron economy as both conservative and defensive, on the one hand responsive to the cellular metabolic needs and on the other "protective" so as to minimize potential damage due to labile iron exposure to oxidative conditions.

How does a regulated absorption maintain systemic iron homeostasis?

In order for absorption to act as balancing tool (to compensate for uncontrolled losses) it must lean on the surveillance of systemic iron levels expressed in plasma, the body fluid where iron is delivered from the duodenum and from where it is distributed to all tissues. As all plasma iron gets swiftly and tightly

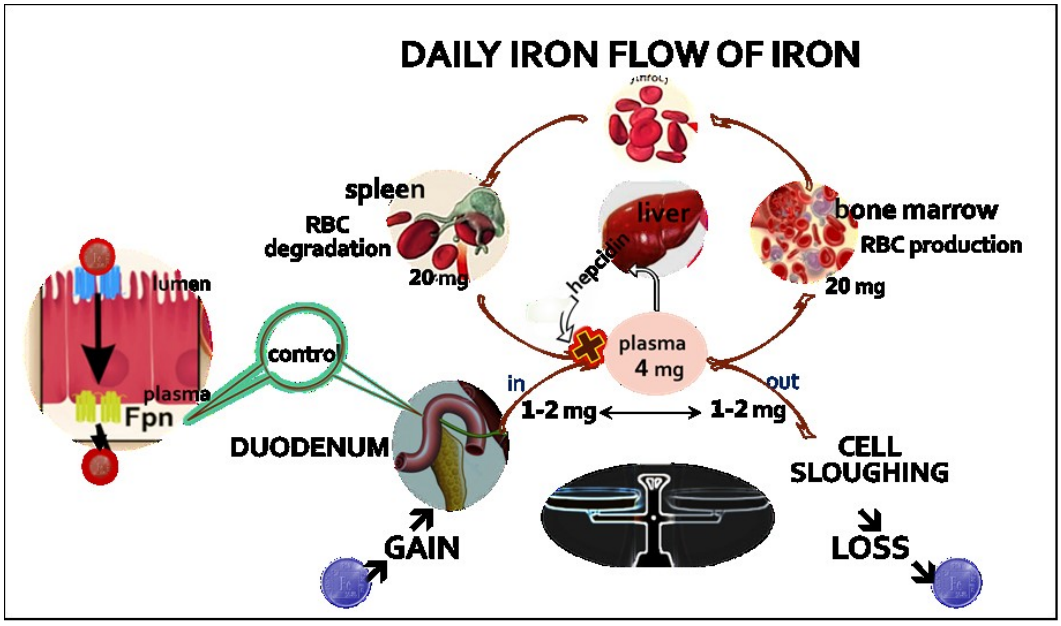
Regulation of iron absorption

Iron ($Fe^{+2\ or+3}$) present in food, is solubilized and extracted in the acid gastric environment following partial proteolytic digestion. Interference with the gastric acidity will render the iron less available for absorption, together with chelating molecules present at relative high levels in different food sources. Iron absorption is restricted to the duodenum and the transport into the cells limited by the enzymatic conversion of Fe^{+3} to Fe^{+2}at the mucosal surface. That reductive activity together with the relevant trans-epithelial iron transporters are negatively regulated: a. systemically by the hormone hepcidin secreted by the liver in response to plasma transferrin iron saturation (TSAT) and b. locally by mucosal cell iron and oxia (sensitive to substances secreted by the microbiome).



associated with circulating transferrin, whose iron saturation level (usually represented in terms of % saturation or TSAT) is sensed by hepatocytes, that in turn respond by triggering the synthesis and secretion of the hormone hepcidin, the master regulator of iron gates into circulation. The two physiological entry gates are identified with ferroportin (FPN), the iron exporter that is expressed

primarily: a. in duodenocytes involved in daily absorbing 1-2 mg iron and b. in reticuloendothelial cells of spleen and liver involved in recycling 20 mg/d iron from phagocytized red blood cells (that represent 1% of blood cells replaced daily). However, it is the duodenum juxtaposed to the stomach that absorbs the soluble metal (in its ionic form and/or as part of heme, from where it is released enzymatically) and transfers it to the systemic circulation by FPN. That transporter serves as the major controller of iron



traffic into circulation as its expression is largely determined by hepcidin's ability to dock on it and trigger its degradation. Thus the human systemic ferrostat (in analogy to *thermostat TS*) relies on a negative feed mechanism whereby receptors in hepatocytes serve as sensors of plasma iron levels (*temperature in TS*), hepcidin as signal transducers (*electric switch in TH*) and FPN as target executor (*heater in THS*).

Doe the gut microbiome also have a role in iron absorption?

Although the major microbial gut repertoire (microbiome) resides in the large intestine, a significant fraction dwelling in the small intestine is likely to affect the duodenal iron absorption. Indeed, small molecules secreted by some *lactobacilli* species act on duodenal hypoxia-inducible factor HIF2α that can modulate the levels of cell ferritin expression and thereby control the transfer of iron from the mucosal to serosal surface, from where iron is translocated into the main circulation.

Is chronic ID the price of a faulty or a protective iron economy?

Many inflammatory disorders (not only of infective origin) lead to ID and IDA due to poor expression of the iron gates, even when plasma iron levels are markedly lower than normal. This common phenomenon is associated with a rise in pro-inflammatory cytokines that trigger a major hepcidin secretion via cognate hepatic receptors and ensuing hormone-induced degradation of FPN. Some scientists hypothesized that by reducing plasma iron levels via cytokine- induced blockade of iron entry gates into circulation and stimulated withdrawal into liver, the organism acquires a so called "nutritional immunity" from invading pathogens at the expense of systemic ID. Such protective mechanism, if persistent, might also be self-defeating, not only because ensuing organ damage due to ID and IDA but

also because the organs in which iron is accumulated (liver and spleen) might become targets of intracellular pathogens.

However, various other conditions might result in ID, from Helicobacter pylori, gastritis of autoimmune or iatrogenic origin to a sub-functional duodenal surface that results from bariatric surgery or from a hyper-peristaltic gut-flow, all minimally responsive to oral iron as in the inherited disorder IRIDA (iron-refractory-iron deficiency anemia). Obviously, whenever feasible, the therapeutic goal is to address the causative factor of the ID. First and foremost is to eliminate the possible contribution of absorption-interfering factors such as intake of antiacids (including PPIs) or natural chelating entities found in green vegetables, fruits and cereals (e.g. oxalate, polyphenols and phytic acid, respectively).

Clinical treatment of chronic inflammation per se and other ID- or IDA-causing disorders, had thus far only a limited success in restoring systemic iron distribution. The acceptable and widely used treatment of extreme ID has been iv iron supplementation (IVIS), a tool based on iv iron formulations that have become increasingly safer and more efficient. However, IVIS is regularly done in clinical centers under medical supervision and it is counter-indicated during active infection and limited in the pediatric and geriatric population.

How to cope with iron deficiency (ID)anemia in corona days

A salient feature of COVID-19 infection is a storm of cytokines that sweep the organism and is accompanied by a rise in the serum levels of ferritin, a widely recognized acute phase reactant. As the levels of those inflammatory factors are demonstrably commensurate with the severity of the disease, they are often used as diagnostic tools to assess the disease status. As stated above, pro-inflammatory cytokines affect body iron levels by blocking all iron gates to circulation and lead to a progressive iron-deficiency (ID) and ensuing anemia (referred as IDA). The ID results into increased physical weakness and major fatigue even preceding anemia, and over time, to organ damage, especially the heart.

How in corona days does one cope with ID/IDA that is refractory to oral iron supplementation?

The recommended treatment in normal times has relied on periodic infusions of intravenous iron (IVI), but those are generally counter-indicated during the active phase of bacterial or viral infections. Moreover, although IVI are indicated post infection, their availability in clinical centers is largely dependent on the limited provision of services in periods of social isolation.

Can alternate treatments substitute for iv iron infusion in corona days (and beyond) ?

With the recent advent of novel iron formulations based on iron (as pyrophosphate salt) encapsulated in special lipid nanoparticle, it has become possible to use the convenient oral administration route to safely and effectively treat a wide variety of iron deficiencies that are refractory to oral iron supplementation. That is because some special liposomal structures can gain entry into the circulatory system (via intestinal M cells), thereby by-passing the blocked physiological entry route and enabling the supply of iron to the various organs, especially the bone marrow (for red blood cell production). The scientifically and clinically proven novel liposomal oral formulation (referred as sucrosomial iron) is a suitable and convenient alternative to intravenous iron infusions for treating a variety of ID disorders of nutritional or inflammatory origin (in Hebrew http://webinarservices.biz/pharmaline15).

How suitable are the novel iron formulations for treating ID anemia in patients with chronic disorders for whom iv-iron supplementation are generally prescribed, but precluded due to limited clinical services and/or counter-indicated during the active stages of the COVID-19 infection?

In all those chronic situations patients might regain faster and improved functionalities with iron supplied by oral formulations endowed with a proven safety and efficacy record in treating IDA in a variety of inflammatory or genetic disorders that affect body iron status. Thus, during periods of restricted clinical services, the novel oral iron treatment can benefit the thousands of ID patients with chronic disorders that become deprived of essential iv-iron infusions.

Practical aspects of oral iron formulations

Oral iron supplements for adults are ordinarily taken daily at doses of up to 120 mg elemental iron (as sulfate salt or as complex with organic acids or sugars) but preferably every other day (to avoid a refractory absorption period that follows any major iron intake). The normal yield of iron absorption is 8-15% depending on the iron complex, but in inflammation it is markedly reduced to only 1-5%. Vitamin C is often recommended as additive so as to aid in the chemical conversion of Fe^{3+} to the membrane permeable Fe^{2+}. Significant Increase in Hb levels in IDA are usually assessed after 4 weeks of oral treatment or 2-3 weeks after IVIS

Daily Sucrosomial iron is given orally in units of 30-60 mg elemental iron during or between meals.

For presentations (written material and videos of lectures) follow:
https://www.bio.huji.ac.il/he/node/9641 (Hebrew); https://www.bio.huji.ac.il/en/content/cabantchik-ioav (English)

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