Cancer Prognostics and Diagnostics (CPD)

Research Project: Part -1

Iron in Initiation and Promotion of Human Cancer -How Free Iron Accelerates Predisposing Insulin Resistance

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Abstract

Iron is physiologically essential for life, but biochemically it is harmful due to its evident-but unappreciated-oxidizing and inflammatory power in tissues when it accumulates, is dosed in excess, or is found free; and this because, after entering the organism, unlike any other metal, its elimination is almost non-existent in man; Thus, the metal is a powerful promoter of chronic degenerative diseases, from diabetes, neurodegeneration to cancer, passing through the extensive coronary and cardio cerebrovascular pathology; modifying its clinical expressiveness and accelerating its severity (Fernández-Real, 2002).

Iron is a powerful oxidizing and inflammatory agent, and its accumulation originates and promotes the proliferation of cancer cells in particular, both in animals and in humans. Free and accumulated iron triggers a powerful Uncontrolled Cellular Proliferation, permanently fueling the survival of the neoplastic cell. After more than 50 years of experimental and preclinical studies, it is clearly demonstrating the carcinogenic power of iron (1); and this is also verified in humans, from breast and endometrial cancer, in women, to cancer of the colon-rectum, prostate, and pancreas in men.

In Western men and women, reductions in iron stores have an important anti-tumor and preventive effect for the development of cancer or diabetes, two biologically interrelated entities due to states of Insulin Resistance, an inflammatory state that favors the development of malignant neoplasms and can accelerate their aggressiveness.

It is the chronic excess of insulin or its Tissue Resistance, the biological event and the clinical syndrome that increases the carcinogenic power of excess iron, both silent epidemics in modern man. Moderate increases in body iron levels increase the risk of acquiring cancer, and raise the degree of its mortality (Stevens, 1994). and its deficiency or chelation in vivo decreases tumor growth (Wang F, Elliott RL, Head JF: Inhibitory effect of deferoxamine mesylate and low iron diet on the 13762NF rat mammary adenocarcinoma Anticancer Res. 1999 Jan-Feb;19(1A):445 -fifty). If excess iron mediates and increases the risk of cancer associated with insulin resistance, all subjects with this syndrome can minimize any associated health risk (and their increased risk of cancer) by avoiding iron-rich diets and donating blood with regularity (McCarty, 2003); since iron in charge is the metal that causes "spontaneous" and point mutations and gene fusion through chromosomal translocations, constituting the greatest risk factor for human carcinogenesis (McCarthy, 2003, Toyokuni, 2014, Wang, 2018). "The excess of blood formed elements is the cause of fatal metastases" (Fouaine, 2016), given the discovered carcinogenic effect of platelets and neutrophils (Saito, R. et al. Platelets enhance malignant behaviors of gastric cancer cells via direct contacts. Br J Cancer 2021;124, 570, Rapoport, Role of the Neutrophil in the Pathogenesis of Advanced Cancer and Impaired Responsiveness to Therapy.

Molecules. 2020; 25(7):1618).

Iron is physiologically essential for life but biochemically dangerous. Chronic accumulation of iron causes pantropic organ damage and excess body iron play an important role in carcinogenesis, coronary artery disease, neurodegenerative disease, stroke. and inflammatory disorders. Iron is very slowly excreted from humans once it is absorbed into the body.

The significance of iron excess has been markedly underestimated, despite the fact that iron overloading disorders are as commonplace in the US white population (Conrad, 2002). Iron-overload and catalytic iron promotes activation oxidative responsive transcription factors and pro-inflammatory cytokines that increase cancer extension and aggravate them. There is accumulative evidence for iron as a carcinogenic metal in epidemiological, clinical, animal, and cell culture studies. The role of iron in various cancers, such cancer was demonstrated. Recent advancements on the molecular mechanisms of iron colorectal and liver as carcinogenesis evolved the Insulin-resistance generation and promotion, fisiopatologic condition that is not only permissive, but be generated cancer and promoting it. May nutritional metals, iron is highly conserved: toxicity due excess iron can occur either acutely to Unlike other after a single dose or chronically due to excessive accumulation in the body from diet. Live studies have demonstrated that an iron deficiency induced by either feeding low iron diet a injecting the iron chelator deferoxamine mesylate decreases tumor growth (Wang F, Elliott RL,Head JF:Inhibitory effect of deferoxamine mesylate and low iron diet on the 13762NF rat mammary adenocarcinoma Anticancer Res. 1999 Jan-Feb;19(1A):445-50).Iron supplementation has at times proven ineffective and even detrimental to health (Dao, 2013).Thus, iron excess may mediate the increased cancer risk associated with insulin resistance and heme-rich diets, and subjects who are insulin resistant can minimize any health risk associated with iron overload by avoiding heme-rich flesh foods and donating blood regularly (McCarty, 2003). The energy that sustains cancer cells derived preferentially from glycolysis (Matoba, 2006) depends on the p53 deficiency-iron induced. This nutrient is postulated to gene contribute to the initiation of in vivo (Nakano 2003, Tuomainen 2007, Rockfield, 2017), cancer

but iron overload initiates and sustain cancer development if chronic infection insulin or resistance conditions are present.

Cancer cells require considerably more iron than normal cells. Since iron catalytic can induce driver point mutation and create fusion genes through chromosomal translocations, iron overload is of the most important risk factors in human one carcinogenesis (Toyokuni, 2014). Because free iron may play a catalytic role in "spontaneous"mutagenesis, moderately elevated iron stores increased overall risk for cáncer (McCarthy, 2003). Overactivity of inflammatory cytokines is responsible for anemia of inflammation in different chronic diseases and cancer (Vela, J Transl Med. 2018), and exogenous iron is ever detrimental in sickness. In US, a daily intake of dietary iron more than 18 mg is associated with an increased risk of cancer (Manous, 2014).Daily iron accumulation can be extremely toxic for the body and may promotes carcinogenesis and metastasis or neurodegeneration in the absence of iron chelation therapy (Isidori, Blood R, 2018, Wang, 2018, rev; Fouaine, 2016, rev; Sripetchwandee, 2014).Iron and Neutrophil depletion improved tumor response to chemo radiotherapy (Rapoport, 2020, rev) and inhibited cancer metastasis and metastatic growth (Liang, Proc Natl Acad Sci U S A. 2018 Oct 23;115(43)) (Wu, Front.Immunol.,24September2020)

https://www.pnas.org/content/115/43/11060.longhttps://www.frontiersin.org/articles/1.3389/fimmu.2020.565165/full

Introduction

Iron is a carcinogen (1,2) and cocarcinogen (3,4,5), and strongly increases the risk of cancer in animals (1,2,3,4,5,6); and its cancer-inducing power in animals and humans (6) is rapidly cumulative; reversing neoplastic histological changes in the presence of physiological diets low in iron (7): it has been shown in animals that diets low in iron can slow the progression of cancer (7).

It is fully proven that exogenous iron plays a transcendental role in cell proliferation and tumorigenesis (8, 9, 10, 11, 12, 13, 14,15), and this is explained by the "inflammatory and mutagenic accumulation" that occurs and it is greatly strengthened over time – iron is the only metal that is practically not eliminated; except in menstruation (1)-: just a low dose of oral iron increases the generation of free radicals and systemic inflammation in the feces of healthy subjects (16).

Free iron, which increases markedly in the presence of the superoxide radical, is "persé" cytotoxic, mutagenic and carcinogenic (1); being able to cause an acceleration of arterial thrombosis by directly altering the coagulation systems and vascular (17,18) and platelet (19) reactivity. Iron directly activates the nuclear transcription factor NFkB, which initiates a cascade of inflammatory activation; and it also stimulates the secretion of interleukin IL-1 in macrophages (stimulated by LPS); and its overload, on the contrary, inhibits the expression of inflammatory cytokines (20) necessary for tumor suppression (see below). Actually, the damage to cellular DNA that occurs under pro-oxidant conditions is mediated by iron, which can initiate (9, 21) or increase (1, 21) pre-mutagenic and pre-malignant damage, and which is become powerfully carcinogenic (10, 8, 9) due to its tissue and dietary overload (5, 8, 9).

Why is Iron Carcinogenic Today? The Forgotten Evidence

Iron is a vital metal for life, but it is potentially harmful, as it promotes the hydroxyl radical, the most reactive of free radicals, for which it generates considerable oxidative stress and tissue inflammation (1); and since it is not eliminated, except in physiological menstruation, it slowly and progressively accumulates in the body, causing a vicious circle of inflammation and degeneration, in light of the current nutritional inflammatory aggression. Specifically, accumulated body iron is directly and powerfully related to the original appearance or promotion of neoplasias, cancer, and the increased risk of mortality (1-10).Physiologically, the adequate use of iron and the defense for its accumulation are found in the Transferrin transporter protein, proven anti-inflammatory; and in cellular Ferritin, which initially constitutes a defense against latent iron damage (1, 10).The superoxide radical, which is physiologically increased in the current systemic (nutritional) inflammation situation, is a powerful factor that increases the release of iron from its binding molecules: lactoferrin, transferrin, ferritin or hemosiderin (1).

For more than 25 years, it has been completely proven that iron fuels the survival and growth of cancer cells above normal cells (1, 22, 3); by promoting the accelerated generation of reactive oxygen species, which have a crucial role in chronic pathology, from atherosclerosis to neurodegenerative diseases (7, 10, 8, 9, 1). For this reason, pathological situations of abnormal iron accumulation, such as Hemochromatosis, are accompanied by a high frequency of neoplasms (1).

In the first National Health and Nutrition Examination Survey (started in 1971; and followed up between 1981 and 1984) it was verified in more than 14,000 patients that the body iron status (measured as transferrin saturation, its transport protein in plasma) increased the cancer risk in men (22); and then, by extending its follow-up until 1988, it was evidenced that in both sexes (3,287 men and 5,269 women), the highest risk of cancer occurrence -and death- occurred with only moderate levels of iron (23). And this is because a very slight excess of unused iron is enough for it to be used more efficiently by neoplastic cells (or pathogenic microorganisms) (3,1).

Iron in dietary overload is a decisive cofactor for the development and maintenance of any disease (24, rev, 25, rev). For example, even in the presence of normal iron stores, a simple exogenous ingestion of iron increases the risk of infection (26, 24), and this, specifically, by increasing Insulin Resistance, -the hormonal event that predicts Chronic Disease. -, and for being a powerful activator of the NFkB factor, whose signaling is increasingly recognized as decisive in the promotion of tumorigenesis: NFkB is a powerful factor that confers resistance to the programmed death of the tumor cell; that is, it is a potent anti- apoptotic, conferring survival to the npeoowpelar s(2ti7c)c. eIfllleaunkdepmroicmcoetlilnsgpirtoslimfeeratatesteaaticsily in an iron-rich environment (28), the common epithelial neoplastic cell that feeds almost exclusively on cellular iron (7, 3,4,5, 8, 10, 22, 24, 25).

Iron Reserves, Onset, Progression and Mortality from Cancer: The hidden evidence

As we have pointed out before the physiological, experimental and epidemiological evidence, the rapidly growing neoplastic cells feed on iron; the greater its tissue availability, the greater its growth (without differentiation); and conversely, iron deprivation produces a pronounced effect on neoplastic cell proliferation (7).However, it has been known for more than 50 years - Richmond, 1959 -that exogenous iron loads rapidly produce, and de novo, sarcomas in vivo (1); After almost 20 years, in which there was an inexplicable silence on the matter, today it has been

irrefutably demonstrated in vivo that a "normal" diet of iron promotes breast cancer in humans (29). And this happens, for approx. Five years and a half, where in this part of the world (and Latin America) everything that is offered to us for “better health” has absorbable iron supplements (24); inflammatory and promoter of carcinogenic oxidative stress), which, “normally”, today, humans damage their cellular nuclear DNA (21, 8, 10, 20) and are exposed to rapid cancer-promoting mutagenesis (1, 8, 10).

A single example, in the most aggressive cancer: in 113 children with Acute Myeloblastic Leukemia, those who had higher iron stores -measured as Transferrin Saturation, or Serum Ferritin- had a significantly lower Survival (at 2-year follow-up). , with a higher index of organomegaly ($p<0.001$) (28).This largely explains why the rate, for example, of breast cancer has increased resoundingly in the Asian continent; but especially among Chinese immigrants in the USA, where neoplasia-promoting environmental aggressors have changed drastically (29): again, iron stores increase the risk of pre-neoplastic transformation of healthy mammary epithelium (29) (fibrocystic changes); and dietary iron intake, but alone, increase the risk of progression of these fibrocystic lesions to cancer (29).This is corroborated in another cohort study among more than 9,000 women with benign fibrocystic breast disease, in which a moderate elevation of breast tissue iron predicted an increase in cancer (30).So, it is verified in humans that elevated body iron stores increase the risk of cancer (22,24) and its mortality (23, 24, 25); In addition, and this is a very important epidemiological determinant, iron deposits such as serum ferritin confer a greater risk in general morbidity and mortality (31); but with special relevance in cardiovascular pathology (32), by slowly but profoundly damaging the quality of one of the most pleomorphic and protective hormones in our body: insulin (31): it is its deficient tissue action -Insulin Resistance- the hormonal event that predicts suffering from Chronic Diseases, (33, 34), from cardiovascular disease to cancer (see below).

Mursu et al. have shown that mineral and vitamin supplementation is associated with increased mortality, and this is mainly due to added iron (Backe MB, Moen IW, Ellervik C, Hansen JB, Mandrup-Poulsen T. Annu Rev Nutr. 2016 Jul 17:36:241-73. https://www.annualreviews.org/doi/10.1146/annurev-nutr-071715-050939?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed.

Cancer Nutrition. When Iron becomes our Killer.

The post-prandial increase in glucose is a crucial and causal determinant for the development of cardiovascular disease (35), as it is the expression of a Hidden Insulin Resistance (34) that promotes disease (33) (even in non-diabetics). And all this metabolic alteration is due to excess oxidizing iron, one of the most powerful generators of free radicals in vivo (36), activator of the most powerful inflammatory factor NFkB (20) and, therefore, inducer of insulin resistance in tissue. hepatic (37), adipose and vascular (31).It has been shown that the reduction of iron reserves by donating blood, even in healthy subjects -with normal ferritin levels- (31) prevents the appearance of Type 2 Diabetes Mellitus (DM 2); and ostensibly improves vascular function, improving hemodynamic parameters by reducing oxidative stress (32) and systemic inflammation; reducing cardiovascular and metabolic risk (32, 31).Subjects with even mild anemia improve their cardiovascular hemodynamics by donating blood, according to the demonstration by Hod et al. (Blood, 2022)

https://medicalxpress.com/news/2022-09-donor-iron-deficiency-effectsblood.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily nwletter

Humans with GE reflux and high iron intakes can develop esophageal adenocarcinoma by increasing chronic inflammation (and the production of reactive nitrogen species) by the esophageal epithelium (38), which reinforces the concept that persistent oxidative damage causes, and explains the biological changes that occur in the cancer cell (38,39): "persistent oxidative stress and chronic inflammation as a generator of cancer" (39). It has long been demonstrated that a local iron overload is directly responsible for promoting carcinogenesis (10, 38, 2, 3, 4, 5, 6, 7, 8); and systemically, rapidly and cumulatively, exogenous iron is a powerful potential initiator from liver damage; being able to play a determining role for the generation of chronic fibrosis or acute liver toxicity (40).

Extraction of Iron is Protective of Tissue Damage and Cancer

When Iron Retention Facilitates Tumor Development.

Iron must be used, not retained, and not accumulated in excess: iron retention prepares and facilitates tumor proliferation (41), both inside and outside the cell; and it is supported by the biological fact that in all dysplastic or dysplastic tissue there are greater transferrin receptors as a defense mechanism against the perennial aggression of the surrounding deposited and free iron (39, 40).

There is accumulating evidence that reduction of systemic iron by phlebotomy or by donation substantially reduces visceral malignancies and mortality in patients with peripheral arterial disease (42) or arterial hypertension (insulin resistance) (43).An iron-deficient diet is effective in effectively reducing acute liver damage and chronic liver fibrosis in animal models (40) and clinically, this has been demonstrated in humans with hepatitis C (see below).Again, the growth and nutrition of cancer cells is powerfully promoted by the exogenous administration of iron; and it is retarded by its dietary deprivation (24,25); specifically by directly activating iron signaling the NFkB factor in macrophages (20), especially when it is intracellular (44); and it is the NFkB factor that controls and ultimately determines the genes for proliferation, angiogenesis and metastasis (41), constituting a powerful anti-apoptotic factor (20), just like insulin (33). Furthermore, this transcription factor is the molecular key that links inflammation with carcinogenesis (41).And if we remember now that insulin is the anabolic hormone whose signaling disinhibits and activates this kappa-B carcinogenic factor; the oncogenic circle is permanently activated.Regarding the carcinogenic power of iron stores, and like the insurmountable advantages of phlebotomy or blood donation, the agents that capture iron, iron chelators have become (for more than a decade) an effective method in reducing cancer (45-47), and above all with an advantage over other treatments with serious side effects, since the development of lipophilic chelators that capture intracellular iron can kill cancer cells selectively, without damaging normal tissue (47).

Iron and Oxidative Stress as Initiators and Promoters of Cancer

It is biologically, experimentally and epidemiologically established that iron overload contributes decisively to the generation of cancer in humans (24,25), particularly colon-rectum. Intracellular iron promotes genomic instability, rearrangement at the chromosomal level, and double mutation of both proto- oncogenes and tumor suppressor genes (41). What's more: to at physiologically minimum achievable concentrations (200-500 micromoles), iron increases genetic damage 2-3 times over control (48, 49).

This remains largely patented in normal humans, where only 19 mg. of iron sulfate cause damage to the colonic mucosa due to the iron-dependent increase in the synthesis of ROS free radicals, potentially inflammatory and oncogenic (16); Worse still, if ferrous sulfate is administered together with vitamin C, at doses as low as 14 mg/day, it increases oxidative damage in leukocytes from healthy subjects (50). This indicates that the mutagenic damage exerted by DNA oxidation occurs with the simple exogenous addition of absorbed and non- absorbed iron. The greater the cellular and tissue availability of iron, would there be greater cell proliferation? The answer is undoubtedly yes. The overexpression/induction of transferrin receptors with “uncontrolled” cell proliferation (51) is clearly established, both in leukemic cells and in esophageal cells (38).If, as has been shown in vivo, high body iron stores reduce survival in childhood patients with acute leukemia, probably by increasing the rate and extent of the disease (28), its neutralization by chelation, causing cell death. neoplastic (52).

The first iron chelating agent (developed more than 3 decades ago), Deferoxamine has recently shown that, in a promising dose-response efficacy, it induces the programmed death -apoptosis- of leukemic cells, by reducing the intracellular pool of labile iron, that it exerted an anti-apoptotic survival power; and intracellular iron deprivation activates caspase-dependent apoptotic cascades) (53, 52).

Cytosolic free iron deprivation inhibits tumor growth through mitochondrial expression of ferritin (54), as has just been demonstrated, reliably in vivo. Biologically, only cellular iron deprivation will reduce tumor growth and proliferation, because it has been long demonstrated in vitro and in vivo, in animals and humans, that cancer is a pathology derived from iron toxicity (55, 10).

It has been known for more than 3 decades that iron-chelating drugs have antiproliferative properties (56), restoring the alteration in the cell cycle caused by free iron (57), which profoundly favors the proliferation of neoplastic cells; and, what is worse, its premalignant transformation from normal cells by cumulative DNA damage (10, 8, 1, 24).

This is biologically verified with iron deprivation that causes cancer cell apoptosis (57), and the consequent regression of the tumor due to an iron- deficient diet, verified in vivo (54). Today it has been shown that intracellular iron, or its overload (when it exceeds the anti-inflammatory protective mechanisms in serum -transferrin- and tissues -ferritin- to name the best known), profoundly alters the physiological cell cycle in normal liver cells (58 , 59). It is for this particular reason that all "breakthrough" cancer treatments have such a high rate of failures, since the iron-rich tissue environment confers a high degree of tumor resistance (57).

Precisely, given its enormous avidity for iron, for its optimal nutrition, growth and proliferation, iron chelating agents are increasingly emerging as an effective and efficient therapy for the ideal treatment against cancer (60-

63).In a biologically determining way, iron protects the survival of tumor tissue (60), exerting a clear carcinogenic activity and promoter of neoplastic growth; particularly by neutralizing the bactericidal and antitumor action of macrophages (64, 10).

Today, in the extremely common presence of tissue and environmental inflammation (diet, infections, genetic resistance to insulin or familial diabetes); iron becomes a powerful cellular and tissue oxidant (39, 10, 1), by catalyzing the most powerful reactive oxygen species, the hydroxyl radical (1,10), a powerful inducer of cancer (39, 36, 48, 1, 10, 7) animal (36, 7) and human (48).

Therefore, iron greatly enhances both the risk of initiating a neoplastic transformation, by originating and promoting a genetic modification and an active and permanent inflammation and proliferation (65, 39, 41) that generates human cancer.

Current Iron as Promoter and Aggravator of Disease: Its Role in Chronic Inflammation

If marked clinical oxidative stress is known to occur following a parenteral iron infusion, it is not surprising that a systemic inflammatory reaction occurs acutely after a single intravenous injection of iron, aggravating experimental sepsis (66).

Interestingly, exogenous iron is rapidly deposited in any tissue that presents previous inflammation (38); and in turn, chronic inflammation is an extraordinary breeding ground for the appearance of neoplasia (67), since it rapidly activates the Wnt oncogenic signaling necessary for the development of epithelial cancer (68, rev).

Models of esophagoduodenal anastomosis that are exposed only once to iron develop neoplasia and cancer (38); and this is verified again in humans, where a single dose of exogenous iron causes cancer (15,14). And it is that iron is directly a cellular mitogen (9); in particular in conditions in which there is a permanent exposure to environmental inflammatory aggressions: several epidemiological studies have verified that chronic elevated iron plays an important role in the genesis of lung cancer (70, 71, 72), both in its initiation and in their progression (71, 72) respectively.

The clinical verification that indicates that all parenteral administration of iron, powerfully cytotoxic, varies directly according to the release and tissue uptake of iron is very relevant (73); and that it is potentially damaging to the kidneys because it causes glomerular endothelial damage, and progressively interstitial nephritis.

Very interesting: fulminant hepatitis can be prevented with iron restriction as,demonstrated in animal models of genetic copper accumulation (Wilson's disease); indicating a potent acute cytotoxic synergy between the two metals (74).By the way, it is widely proven that in Hemochromatosis (abnormal tissue iron accumulation) the incidence of liver and breast carcinomas is extremely high (25, 10, 24).It has been strongly suggested that lower dietary iron intake, and in particular, lower body iron status, reduces the risk of acquiring prostate, lung, colon (colon- rectum) and ovarian cancer (75).

If the excessive accumulation of copper and iron is a proven cause of liver cancer in animals and humans (76, 77), respectively, the "simple" mild hepatic iron overload causes hepatic resistance to insulin (by interfering with its proper anti- insulin signaling). inflammatory and antigluconeogenic), in such a way that the iron load is the cause of Non-Alcoholic Fatty Liver (NASH); and its reducing therapy (dietary or by phlebotomy) can reduce the high risk of hepatocellular carcinoma (78), and especially in subjects with Insulin Resistance (IR).

Definitely, lipid peroxidation and the generated accumulation of oxidative stress cause cancer in genetic Hemochromatosis (79).The accumulation of the marker of oxidative damage to DNA, 8-hydroxy-2ÿ-deoxyguanosine (8-OHdG) (79), which occurs as a result of a continuous generation of ROS (chronic inflammation) has been reported in preneoplastic lesions and in cancerous tissues (80); In this regard, and fascinatingly, it has been irrefutably proven that short- and long-term iron-reducing therapy (78, 80), respectively, reduces this DNA oxidation product in nonalcoholic steatohepatitis NASH (78) and in chronic hepatitis C (80).

So, once again, it is strongly proven that increasing the body's iron stores damages cellular DNA; and that phlebotomy, in addition to reducing the increase in liver enzymes, reverses DNA damage -measured by 8oxodG- (78); therefore, Oral Iron restriction or Phlebotomy reduces the risk of liver cancer in subjects with NASH (78) and in those with hepatitis C (80). In addition, iron-reducing therapy will reduce chronic (dysplasia-inducing) inflammation dependent on oxidative stress and lipid peroxidation caused by free iron.

Phlebotomy as a Cancer Preventive: The Hepatic Evidence

Just as oral iron depletion slows the aggressive progression of skin cancer (7), phlebotomy (coupled with reduced dietary iron intake) has been shown to significantly reduce the risk of acquiring hepatocellular carcinoma in humans. in patients with hepatitis C (81), by reversing oxidative damage to cellular DNA (80).

Knowing that an iron-rich environment -high transferrin saturation and ferritin levels- powerfully favors the growth of leukemia cells, in more than 100 children with ALL -Acute Lymphoblastic Leukemia- a lower incidence of mortality (greater survival) was found among those children with low transferrin saturation (<36) and lower ferritin levels ($p<0.001$) (28).

This study is corroborated with other clinical studies. Higher amounts of serum and tissue iron are associated with a poorer prognosis for numerous malignant neoplasms (1), appearing as a powerful risk factor for more aggressive cancers such as childhood Hodckin lymphoma (82), neuroblastoma (83) and acute lymphocytic leukemia (1).

With all the biological, experimental, epidemiological and clinical evidence, to this day, it should be known that the suppression of dietary iron (especially animals, Heme) reduces the risk of cancer in the endometrium (84) and breast (85) and colon-rectum (86), particularly in subjects with excess insulin. And it is iron overload, which increases the levels of this hormone (reducing its catabolism in the liver), and reduces its action; and insulin (directly and indirectly) increases the tissue uptake of the metal (31), giving rise to a feared vicious circle of oxidative stress inflammation-proliferation-inflammation-oncogenesis. Experimental lesions in the endometrium show (87), as in

other metaplastic tissues, epithelial cell proliferation under iron load; and this is substantially increased in the presence of insulin.

Insulin resistance, pathophysiologically indicated by reduced Adiponectin, has been proven to be a clear independent factor increasing the risk of breast and endometrial cancer (88, 89), respectively. And, precisely, it is free iron that reduces the production of adiponectin (90) - the only adipocytokine that increases hepatic insulin sensitivity (91), and that can, through various mechanisms, reduce the inflammatory risk of cancer (see forward).

As we have seen previously, iron depletion by phlebotomy produces a significant improvement in insulin resistance, but independently among subjects with metabolic syndrome and fatty liver (92), because it ostensibly improves glucose uptake by improving hepatic signaling. of insulin and improve its receptors (93). https://www.eurekaselect.com/178835/article Dysmetabolic Iron Overload in Metabolic Syndrome, Sachinidis, 2020 (see end).

Thus, it is verified -in vivo and in vitro- that iron depletion improves glucose clearance, while its oral administration reduces it; by this mechanism, too, phlebotomy and blood donation can significantly reduce the occurrence of diabetes and cancer (see below). And it is that, as has been recently verified, dietary iron overload induces Visceral Insulin Resistance (93).

Diabetes and Cancer: The Iron Connection

Elevated iron deposits such as Ferritin are today part of the Insulin Resistance Syndrome (Metabolic Syndrome: Dyslipidemia, Arterial Hypertension and Central Obesity) (94); and this syndrome, a true epidemic of the century and a predictor of chronic disease (34), is strongly associated with the presentation of neoplasia.

The iron-insulin-glucose relationship is very exciting: if free iron profoundly alters glucose metabolism, on the other hand, it interferes with the hepatic clearance of insulin, causing its increase and reducing its sensitivity (iron reduces glucose uptake by the fat cell, see later). And insulin also increases the synthesis and deposits of ferritin, by inducing cellular iron uptake –in parallel to glucose uptake) (95). So, excessive iron becomes a powerful hyperinsulinemia-inducing factor, and by this mechanism alone, it becomes an indirect factor that favors the survival (anti-apoptosis) of cancer cells.

We now know that elevated insulin levels, like insulin resistance, independently (of obesity and other risk factors) increase the development and progression of cancer (96): the hormone is a powerful growth factor in tumor formation, by increasing DNA synthesis and inhibiting neoplastic and cancer cell apoptosis (97).There is overwhelming, accumulating evidence that insulin is linked to the etiology and prognosis of cancer (98, 97, 96); especially in breast cancer (98).But all this, with the hidden presence of tissue iron, which increases the circle of cellular inflammation: Insulin Resistance Hyperinsulinemia->>Insulin resistance.

However, an interesting meta-analysis of epidemiological studies indicates that prospective and cross-sectional studies, especially for breast cancer, hold the suspicion that hyperinsulinemia would generate neoplasia and cancer according to a secondary factor (99); and we bet that this evident preclinical biological and experimental factor is iron.

Coincidentally, premenopausal breast cancer occurs with great frequency in non-obese women – that is, not apparent hyperinsulinemics (98). And it is now known that insulin, physiologically, when it has good sensitivity and is not chronically elevated, can even be protective against cancer by activating the IGFB-3 protein (IGF-1 binding factor), and have a global apoptotic effect (96). Accumulated iron, potentially carcinogenic, is essential for cancer to appear.

It is widely known that diabetes or glucose intolerance are predictors of a poor prognosis in cancer, in addition to powerfully increasing its risk (100), (both due to insulin resistance and glucose toxicity); and this occurs, despite reductions in insulinemia; therefore, the metabolic toxic link, we categorically affirm, is iron (101); In accordance with this, it is evident that hepatocellular cancer, that with immense iron accumulation power, is the malignant neoplasm with the worst prognosis in subjects with diabetes and glucose intolerance (100).

Iron in the Pathogenesis of Type 2 Diabetes: A Path to Neoplasia?

Cumulative epidemiological, experimental and clinical evidence proves that it is Animal iron (Heme) and supplemental added iron, which increases ferritin reserves, chronic oxidative stress, and directly and indirectly confers an increased risk of type 2 Diabetes Mellitus. (102) in populations healthy.

The lower muscular uptake of glucose (101) due to the high iron reserves, explain by themselves its causal effect in the generation of hyperglycemia with hyperinsulinemia (103); and extensive oxidative-inflammatory tissue damage is a potential cause of diabetes (104) and chronic disease (105), due to causing (and aggravating) insulin resistance, the predictive, disease-promoting hormonal constellation (33, 34).

As we have pointed out, the coexistence of diabetes and cancer is very high: for diabetes to appear initially, there would be a preferential deposit of iron in pancreatic cells with apoptosis of beta cells and excessive deposit of pancreatic collagen (106); relative insufficiency in insulin secretion would add to systemic and hepatic insulin resistance, triggering DM2.

Glucose Intolerance in Cancer: Is Hidden Diabetes the Path to Neoplasia?

Naturally, not all cases of adult-onset diabetes follow the same evolution, nor do they present the same pancreatic reserve: we affirm that the greater the residual capacity to continue (or increase) chronically excessive insulin levels, the greater the excess will be. cell exposure to mutagenesis and oncogenesis.

In other words, the more "mild" the fasting hyperglycemia is in a diabetic subject (due to greater insulinemia; as long as tissue resistance does not increase ostensibly), the greater the probability of future cancer; instead, diabetes could be protective against aggressive cancer if insulin levels are considerably reduced (autonomic diabetic

neuropathy), and elevated ferritin stores: chronic anemia in a diabetic subject (considerable diabetic nephropathy) would protect the patient from a aggressive cancer (eg pancreatic or breast cancer). Reduced levels of insulin (97) or ferritin (90) have been shown to reduce the risk of cancer; however, if the subject continues to "accumulate" iron, even the current levels of the metal, considered "normal", progressively impair the function of the pancreatic islets (90), given their extreme susceptibility to oxidative damage (106) (as well as than the brain).But, if the patient has a comparatively high tissue (and pancreatic) antioxidant reserve, the chronic excess of free and accumulated iron; and the hyperstimulation of the Insulin-IGFs Axis would (first) generate neoplasia; in particular for maintaining potent antiapoptotic signaling, a determinant for adverse prognosis in cancer, and resistance to therapy (98).

The accumulating evidence is compelling: in humans, iron, insulin resistance, and excess insulin levels are biologically interrelated (95, 31), translating an increase in iron stores, which predispose to iron deficiency. diabetes and cancer (101).There is a high risk of diabetes (103); but particularly cancer in men and women with moderately high iron levels; as verified in a cohort of more than 10,000 subjects, participants in the first National Health and Nutrition Examination Survey (23).In subjects with DM2 -with high ferritin levels- it has been shown that phlebotomies reduced iron storage by approximately 50% (from 460 to 222 ng/ml) Blood glucose levels and insulin sensitivity significantly improved (107).So, in addition to the experimental studies carried out on animals, it is clinically evidenced in men and women, a clear protection of iron losses against the risk of suffering from diabetes (107) and cancer (42).Gestational Diabetes, which seems to be caused by excess body iron accumulated in the third trimester, confers a higher risk of future cancer, as we will see later.

Insulin and Iron in the Initiation and Promotion of Cancer: The Example of Breast Cancer.

Insulin can potentiate the carcinogenic effects of iron, and this seems to be more forceful in women, particularly due to leptin and estrogens, which promote tumor growth (91): in vitro, insulin increases cellular iron uptake by increasing the redistribution of tissue transferrin receptors (108), potentially increasing the nutritional susceptibility of the cancer cell to its iron-dependent growth (1).If insulin itself increases cellular iron uptake (in parallel with glucose uptake), progressively, high levels of free iron (and transferrin) significantly alter glucose transport to adipocytes, promoting their resistance (109) –similar to iron-dependent muscular endurance (see above).

Circulating levels (110, 111) of insulin, and tissue signaling (IGF-1 insulin) are particularly increased in early stages of breast cancer, even in the absence of obesity (91); it is known that central obesity confers a greater risk of cancer (especially in the colon, colon-rectum, endometrium), increasing its mortality (112, 113), respectively; and in all of them the chronic excess of insulin is very relevant as a causal factor (see above).

And this increased cellular exposure to insulin (and iron) occurs before birth: the excess size and weight of girls is a powerful risk factor for breast cancer, which can originate in utero (114). It has been shown that Glucose Intolerance associated with Pregnancy and Gestational Diabetes in the third trimester are caused by excess maternal body iron (115); and as shown in a large prospective study in Israel, it markedly increases the incidence of primary cancer in women (116).

If we have seen that women could cause their future breast cancer in utero, given their greater exposure to various cell proliferation factors, especially insulin and estrogens, the latest studies that indicate that the prognosis of early breast cancer should not be surprising. (Especially in premenopausal women) is closely associated with high plasma insulin levels: the higher the fasting insulin, the worse the cancer prognosis (117, 118).

Both within human breast tumors and in tumor cell lines, a significant increase in receptors for insulin and IGF-1 has been convincingly demonstrated (118, 119); Together with the accumulated evidence, today there is no doubt that insulin is the causal link between excessive caloric intake, free sex steroids and breast cancer (120). In addition, it is Insulin Resistance, particularly, that physiopathogenic event that accelerates the presentation of the tumor (121) and its aggressiveness. And here free (or catalytic) iron has a determining role.

The greater the intake and accumulation of iron, particularly as transferrin, the greater the resistance to muscle and adipose (122) insulin (); and the lower the bioavailability of Adiponectin (88, 90). And the lower the efficacy and protective action of this hormone, the more tumor progression will be favored (91).

Adiponectin: The Hormone that Opposes Cancer.

When Free Iron Eliminates the Last Hope

It has been reported that adiponectin inhibits angiogenesis and neovascularization (91) promoting rapid progression and tumor expansion. Adiponectin, the only "protective" hormone, dependent exclusively on adipose tissue (adipokine), which has exclusive insulin-sensitizing and profoundly anti- inflammatory effects, is greatly reduced in insulin resistance syndromes (hypoadiponectinemia of metabolic syndrome). But, in addition to hyperinsulinemia, free iron depresses adiponectin serum levels by negatively regulating its expression and activity (90).

These findings agree excitingly with reports indicating another powerful potential effect of iron as a cancer-causing agent: in populations not in selected Western patients, a transferrin saturation greater than 60% confers a higher risk of acquiring cancer (122).

And this is particularly due, among other direct factors that damage DNA, to the fact that excess cellular iron reduces (90) the oxidative-inflammatory, antiproliferative and antineoplastic protection of adiponectin (88, 89).It has also been stated, with sufficient biological, epidemiological, experimental and clinical basis, that, in normal subjects -that is, today, with a simple, moderate chronic accumulation of iron as transferrin- the single intake of approx. 19mg of oral iron is , significantly associated with increased risk of cancer (Mainous et al, 2005) (122).

It has been investigated how the expression of genes related to altered iron metabolism are linked to the prognosis of breast cancer (123). Of the 61 genes involved in iron regulation, almost 50% are statistically significantly related to survival in distant metastatic breast cancer (123). And they are profoundly altered by excessive body iron accumulation (10), and naturally, with its high current intake, directly (41, 1, 122, 27) and indirectly (27).

As we initially pointed out, clinically and epidemiologically it has been shown that the increase in body iron stores is strongly associated with a worse prognosis of the most aggressive cancers in humans, such as Neuroblastoma, Hodgkin's Lymphoma or Lymphocytic Leukemia (1). and Acute lymphoblastic, particularly in children (1).

This poor prognosis associated with the increase in tissue iron, and which,as we pointed out before, is associated with numerous acute and chronic pathologies, is explained by generating and maintaining adiponectinemia; and in turn, these reduced circulating levels of adiponectin are associated with an increased risk for invasive (88), breast and endometrial cancer (89, 124); and a considerable delay in diagnosis. Special mention regarding the inverse and independent relationship of adiponectin with the increased risk of colon cancer (see below).

So, the more iron a cancer patient ingests, the more advanced the neoplastic process will be at the time of its detection; and the more aggressive the disease will be (88).In addition to the anti-proliferative, vasoprotective, anti-inflammatory, and insulin- sensitizing actions of Adiponectin (125), the hormone has been shown to have direct inhibitory effects on tumor growth by increasing apoptosis and reducing the rate of cancer proliferation (91, 125,126).Yokota et al. have shown that Adiponectin suppresses the growth of myelocytic tumor cells and induces apoptosis of myelomonocytic leukemic cell lines (126).

Adiponectin signaling directly modulates tumor cell behavior (125); and whether excess insulin increases cancer risk (96, 97, 98, 99,111), abdominal obesity or metabolic syndrome in each of its components does so with much greater intensity (127) due -particularly- to the circulating reduction of adiponectin; originated, promoted and maintained over time by excess free iron. High iron concentrations in adipose tissue negatively regulate serum adiponectin levels and confer greater risk for diabetes (90); Quite the contrary, reducing excess iron (by chelation or dietary restriction) prevents experimental toxicity and the destruction of pancreatic beta cells, and to a large extent, this responds to non-interference in the physiological actions of the adiponectin.

The anti-angiogenic activity exerted by adiponectin is due to its inducing effect of vascular endothelial apoptosis, and its inhibition of cell migration and proliferation (128): the hormone can inhibit tumor growth of transplanted fibrosarcoma in mice (125; 128). Let us remember that, on the contrary, a single parenteral infusion of iron causes the development of sarcomatous tumors (13, 14).

It is noteworthy that the inverse correlation between circulating adiponectin and increased risk of breast cancer (91, 125) is independent of body mass index - overweight or obesity.In this regard, it has been shown, and again independently of body weight, that Adiponectin is inversely correlated with Leptin, the pro-inflammatory adipocytokine par excellence, both in women without neoplasia (129), and particularly in women with endometrial carcinoma (124).

Leptin, clearly correlated with percentage body fat (91, 125), has been reported to control the proliferation of normal and malignant mammary epithelial cells (130), but is a clear growth factor in breast cancer (91) in an inflammatory tissue environment, where pre-adipocytes also synthesize them (in response to inflammatory cytokines such as TNF-x and IL-1b.Weight gain in rodents increases the spontaneous and induced formation of mammary tumors; and it is

that, in addition to increasing insulin, the abundant local production of leptin can induce breast carcinogenesis (131); and this is potentiated intracellularly by tissue iron (132).

Always aggravated by excess iron, the leptin system plays a fundamental role in the pathogenesis and progression of cancer, particularly of the breast and endometrium (133, 131; 134) - premenopausal for the breast, and postmenopausal for the endometrium, respectively.

Leptin, which particularly modulates excess appetite and angiogenesis – due to its powerful stimulation of VEGF (134) is also implicated in the promotion of ovarian (135) and prostate (136) cancer. It was recently shown that Hemoglobin perpetuates inflammation -macrophage activation- in chronically inflamed tissue,promoting carcinogenesis (Kusunoki, 2021, https://link.springer.com/article/10.1007/ s00795-020-00272-4).

Thus, indirectly, the higher the tissue iron, the greater the mitogenic effects of insulin, and particularly of leptin, establishing an inexhaustible broth inflammation-oncogenesis. Hyperinsulinemia or the IR syndrome (elevated ferritin, low adiponectin, see above) induces human cancer through leptin- dependent signaling and mechanisms (137; 138).

Why does Iron prevent Cancer Cell Death?

Its Reduction May Prevent the Appearance of New Oncogenes.

Insulin together with leptin are powerful hormones that stimulate the development and survival of tumor cells, but especially their resistance to treatment (138, 131); even in the presence of estrogen receptor-negative breast cancer cell lines. Basically, excessive iron confers powerful protection to tumor (and bacterial) cells because it reduces macrophage activity and the microbicidal and antitumor release of macrophage-dependent inducible nitric oxide (64).

Naturally, a marked iron deficiency is just as counterproductive; but minimal amounts of iron are enough to exert its superoxide-dependent primary antitumor protective effect. But, if free radicals can naturally protect against tumor cells, their excess quickly causes the opposite effect: it promotes tumor nutrition and growth, initially by suppressing the activity of tumoricidal cellular immunity (1).

The appearance of tumor resistance that increases every day is closely related to the biological evidence that iron is absolutely essential for the nutrition of cancer cells; and that, conversely, iron chelation has been shown to increase and activate the P53 tumor suppressor protein, crucial for the molecular preventive development of cancer (139); and the most relevant to maintain the suppression of new oncogenes – and the antineoplastic molecular prevention (over time). is that iron depletion stabilizes P53 by inducing the accumulation of the HIF factor (hypoxia-inducible factor, determinant for the control of oxygen homeostasis and angiogenesis) (139).

Iron regulates the expression of several proto-oncogenes (n-myc, c-myc) involved in the genesis of neuroblastoma, the most aggressive childhood cancer; and, once again, it is the high ferritin levels present in advanced disease that predict its poor prognosis (139; 140), by continuously stimulating the survival and cell cycle of neoplastic cells.

When tumor cells are full of iron (and with normal oxygen tension), there will be no cell cycle interruption in the cancer cell, nor its apoptosis. The restriction or chelation of the metal effectively interrupts the progression of this cycle (46, 45, 47), exerting anti-proliferative and apoptotic effects that manage to destroy the cancer cell (47); and most importantly, selectively, fully respecting normal cells; given that cancer's avidity for iron -translated into its elevated receptors for transferrin- are very high in the neoplastic cell, compared to the normal one (38, 139).

With the enormous weight of biological, experimental, epidemiological and clinical evidence, the preventive and recuperative treatment of breast cancer, with iron chelation therapy, has been proposed, particularly in postmenopausal women (141). The combination of genes that promote and maintain a low intracellular iron content is associated with a better prognosis in advanced breast cancer (123) (ER positive estrogen + tamoxifen monotherapy).

Now, let's look at a proven biological fact: When free iron in adipose tissue inhibits the only hormone with anti-tumor properties, adiponectin. Preserved levels of adiponectin, (or better, elevated, in the presence of adequate insulin sensitivity) present anti-carcinogenic activity by promoting tumor apoptosis, dependent on caspase enzymes; and reduce angiogenesis of neoplastic tissue (142, 91).

In an interesting prospective cohort study that included more than 51 men -The Health Professionals Hollow Up Study- a strong negative correlation between adiponectin and the risk of colon cancer was found, independently of measures of adiposity and sedentary lifestyle. (143). Ferritin and other iron parameters were not measured. However, we categorically affirm that this strong adiponectinemia found in cancer (88, 89, 124) is due, in the first instance, to excess ferritin and adipose tissue iron (and then to insulin resistance generated).

We must remember that, even with the appearance of new aggressive oncogenes, if there are high levels of adiponectin due to reduced tissue levels of iron (and probably Leptin), the physiological mechanisms that suppress cancer, such as the antitumor protein P53, will not be inactivated (139)., being able to eradicate cancer.

The greater the cell proliferation, the greater the mutation frequency (1, 10); and the more we feed the preneoplastic cell with iron, the higher the biological rate of mutations will be. If you directly modulate the expression of various genes that , At present, Adiponectin is the only hormone that has tested regulate apoptosis and decrease the growth of myelomonocytic tumor cells (126),the less effective the hormone is, and the lower its levels - regardless of the presence of obesity-, the greater Tissue and cellular resistance to insulin will be (144), a clear promoter, first, and a predictor, after cancer (98).In the genetic disruption of Adiponectin causes proliferation of the arterial intima and experimental insulin resistance (145); in the same way as iron: iron depletion by chelation prevents the formation of neointima (coronary restenosis) in animal models of vascular injury, which proves that cell proliferation is iron-dependent (146).

Cancer and Atherosclerosis: The Crucial Intermediation of Iron.

When the inactivation of cancer protective genes (caretaker genes) and/or continued cell proliferation are produced by free iron, a high rate of mutagenesis and progressive carcinogenesis appears (10): Hydroxyl radicals, caused by excess intracellular iron (in its reaction with hydrogen peroxide: Fenton reaction) (1, 10) cause chromosomal damage promoting tumorigenesis (24, 25, 48, 10).

Iron is the most accumulable metal; in such a way that even small exogenous amounts predispose humans to an early appearance of cancer (6).

The biological events that relate Atherosclerosis and Atherothrombosis to Iron are intrinsically different, compared to the interrelationship between Cancer and Iron; but they will help us understand the initiation of uncontrolled proliferation" caused by free iron-dependent oxidative inflammation.

It has long been proven that high transferrin saturation (the protein that binds extracellular iron) powerfully increases the risk of acquiring cancer in humans (22, 23); likewise, higher iron stores (transferrin/Ferritin saturation) are strongly associated with asymptomatic atherosclerosis and its inflammatory parameters (fibrinogen, IL-8) (147).

Active iron is deposited progressively and intensely in places of greatest inflammation (6), its deposit being directly proportional to body content.

There is direct evidence that free iron initiates atherogenesis (148) when it is deposited in the arterial wall: thickening of the arterial intima and vascular muscle cell proliferation are inhibited by iron depletion; and dietary restriction of metal or phlebotomy reduces the size of the atheroma lesion (149, 150, 148) by minimizing its content and intralesional inflammation.

Current parenteral iron therapy in anemic subjects with advanced renal failure has been shown to cause arterial vascular damage (151) and increase carotid atherosclerosis. Physiologically, iron must be mobilized and not accumulated:

Moderate iron loads markedly accelerate thrombus formation after arterial injury (17): iron overload can directly promote thrombosis, by affecting the coagulation system; By profoundly altering vasoreactivity by increasing vascular inflammation, exogenous iron can increase the incidence of cardiovascular events (152), particularly ischemic events (17).

Biological evidence shows that elevated arterial iron promotes platelet instability (148) by powerfully raising vascular endothelial oxidative stress (152, 17, 148).Vascular cell proliferation and in particular migration is iron dependent; and reverts with its depletion (146); whether the induction of ferritin genes occurs early during the formation of an experimental aortic atheroma, and whether the expression of this ferritin persists until advanced lesions in humans (148),The close cause-effect relationship between excessive arterial iron, atherosclerosis, and

ischemic cardiovascular pathology is not surprising (153), considering the massive generation of iron-dependent toxic ROS that capture the basal NO that regulates cell proliferation.

Iron is undoubtedly a powerful cellular mitogen (58); and this, as we pointed out previously, it is verified in numerous experimental and clinical studies that chelation has potential anti-proliferative effects, both in the Neoplastic tumors ( ) as in the experimental reduction of atheroma (148),It has been reported that, in subjects with coronary syndrome, increased levels of circulating ferritin could be predictive of premature coronary obstructive pathology, in men (154), and independently of the presence of diabetes (where the largest iron deposits are found).Experimental iron overloads are capable of increasing cardiac fibrosis induced by Angiotensin-II, and of increasing the de novo formation of the arterial intima (155); while iron chelation attenuates perivascular fibrosis and thickening of the aortic arterial media (148), according to Ishizaka et al.

(It is possible to reverse cardiac hypertrophy by reducing the inflammatory and oxidative iron overload in cardiomyocytes induced by caloric restriction (An, Caloric restriction reverses left ventricular hypertrophy through the regulation of cardiac iron homeostasis in impaired leptin signaling mice. Sci Rep 2020 Apr . 28;10(1):7176 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7188880/

The reduction of heart attacks with blood donation has been clinically and epidemiologically demonstrated (156); The reduction of iron stores by frequent blood draws (32) or by tissue sequestration of iron (157) substantially improves vascular endothelial function, and high oxidative stress, significantly reducing cardiovascular risk (32, 156, 157).

Given that iron stores are harmful due to their progressive increase caused by the current hypercaloric diet (6, 148), it is convenient to keep normal iron stores in a low range to avoid the accelerated progress of atherosclerosis and atherothrombosis.

The dietary increase in Iron Starts Human Cancer, by maintaining a growing Inflammation and irreversible damage to DNA.

Increased cellular iron is highly deleterious, carcinogenic, and de novo genotoxic (158, 159, 10, 1, 160); even in small increments (158). Just a two-fold increase in free iron in reticulo-endothelial cells or macrophages profoundly alters cell signaling, activating the NFkB factor (158, 159), which is profoundly protective of cancer cells and promotes tumorigenesis (27); Furthermore, elevated iron markedly alters normal cell function by “capturing” and neutralizing nitric oxide and its antiproliferative actions (158).

Ferric iron has been shown to be significantly genotoxic (profoundly altering DNA) even in primary human colonic cells, without any transformation; that is, it has been shown to be the initiator of colorectal cancer (160).Like circulating free hemoglobin, iron is powerfully oxidizing and virulent by stimulating bacterial growth, particularly under conditions of acute stress (69).And in the same way, before any dysplastic or pre-cancerous tissue, the faster

the cell growth, the greater and more intense its obligatory demand for iron; in such a way that its deprivation exerts a pronounced effect in the reduction of tumor (7) and pre-tumor proliferation. (160).

In humans, specifically, the lower the body iron stores, the lower the incidence of cancer (75). And, in addition to all of the above, it is now known that iron is potentially a direct cancer-initiating agent (161), particularly liver, by causing cancer in the absence of cirrhosis: chronically generated and iron-dependent reactive oxygen species cause peroxidation lipid; whose products (such as malondialdehyde) profoundly damage protein synthesis, causing promutagenic damage to DNA (by deoxyguanosine residues).

Heme iron, contained in red meat, in addition to its high carcinogenic power in the colon, is increasingly proving to have an influence on the high malignant transformation in the lungs: independently of other confounding factors (obesity, smoking, saturated fats, less intake of vegetables and fruits, etc.), red meat excessively increases the risk of lung cancer in women and men (162, 163), respectively. Clearly, elevated temperatures increase the mutagenic content and profoundly elevate the release and lipo-peroxidative potential of iron (163).

A biologically proven and clinically forgotten determinant event: only free iron is essential, both for the initiation and for the permanence of lipid peroxidation reactions (132), sustaining reactions and permanent –eternal- exacerbation of cell damage. And let's not forget that free iron is increased powerfully in the presence of insulin resistance syndrome (94), a chronic "low-grade" inflammation (33), and as such, the best and longest-lasting breeding ground for proliferation. cancer immortal.

The co-carcinogenic effect of iron has been excessively demonstrated, for many decades, however, it has not been given the crucial and determining role in its progression (as today, in its etiology): For example, the metal added in the diet potentiates the incidence of estrogen-induced mammary and renal tumors; and this would be due, in particular, to the fact that exogenous estrogens increase the accumulation of iron, in vivo, greatly facilitating its cellular uptake (164).

In an interesting case-control study of more than 7,000 Chinese women, it was observed that high animal iron increases the incidence of pre- and post- menopausal breast cancer, but especially in the presence of saturated and monounsaturated fats (85); this neoplastic effect of iron was also observed in relation to endometrial cancer (86) in this group of Asian women.

It is once again confirmed today that serum and dietary iron overload is the clearest and most determining risk factor for the increased risk of breast cancer (165), participating in carcinogenesis, particularly in postmenopausal women (132).Inflammation is a critical and determinant component of tumor progression; And although today it is clear that intense cell proliferation -hormone-dependent: insulin, leptin, estrogens, androgens, GH- by itself is not a cause of cancer, today we know that sustained cell proliferation in an inflammatory tissue environment (such as visceral adipose tissue) with an activated stroma rich in growth factors, and with agents that promote direct DNA damage (such as iron), certainly promote initiation (67) and/or potentiate the risk for acquiring a neoplasm (67, 71, 72).

In humans, the increase in the 8-hydroxy-deoxyguanosine derivative has been found in several inflammatory preneoplastic lesions, from uterine and gastric dysplasia; to colon, lung, breast, and stomach cancer tissues (80).Because the liver contains about 30% of body iron, it is one of the most susceptible to iron-induced mutagenesis (80). As we saw before, an abrupt iron accumulation in the liver of Long-Evans rats develops hepatocellular carcinoma (74).

It has recently been confirmed that the controlled loss of iron is anticancer (101): the FeAST is the first randomized study, where the group with reduced iron -which reduced its ferritin from 122.5 to 79.9 ng/ml- , presented a significant reduction in new tumors at 4.5 years (compared to control group); In addition, among patients who developed new cancers, those who had iron reductions had a significant reduction in overall mortality. It is confirmed, then, that reductions in body iron stores have a potential and powerful anti-tumor effect (101).

We will emphasize here that, in addition to the inflammatory reduction of oxidative stress that causes or enhances neoplasia, the reduction of free and accumulated iron significantly improves anti-neoplasia immunity: free iron profoundly reduces immune surveillance against malignant cell transformation, especially by induce a marked alteration in the efficiency of T lymphocytes (increasing suppressor CD8 and reducing helper CD4) (132).

With a diet low in iron, the prognosis of cancer will be improved, as the therapeutic approach will be significantly improved in the event of an iron-dependent tumor reduction (7).

Free Iron: Our Slow and Progressive Killer, Today When We Alter More and More the Natural Metabolism of Iron.

Current Iron Metabolism is Profoundly Altered, and we collaborate daily with it, for example, by profoundly increasing reactive oxygen and nitrogen species with our current inflammatory diet that alters our protective genes and awakens those that promote neoplasia (166), in Particularly among the population with Insulin Resistance, the predictive syndrome of disease (34); As we pointed out before, insulin resistance is a generator of Chronic Disease in humans (33).

For this reason, free iron, which under ideal conditions -plasma with neutral PH- should be exclusively bound to transferrin (and no more than 30%), is internalized in tissues, damaging nucleic acids and membrane lipids. the cell (167). Thus, a coordinated orchestrated system of protein peptides starts up immediately when iron is released both intracellularly (Ferritin) and extracellularly: transferrin and lactoferrin (plasma sequestration); haptoglobin and hemopexin (bind hemoglobin iron, and Heme iron); in such a way that free iron levels do not cause cell oxidation, inflammation and disease (69).

The saturation of all these catalytic iron “binding” physiological mechanisms (free or redox) leads to accelerated tissue degeneration (167), also present in hereditary iron overloads, such as Hemachromatosis, in which the incidence of cancer (hepatic, esophageal, melanoma, myeloid leukemia) is very high (167). In human metastatic melanoma cells, elevated Ferritin significantly increases their growth and renders them resistant (Baldi A, one that

determines what percentage of free iron will be retained in macrophages, hepatocytes and enterocytes (168): its secretion, strongly stimulated by inflammation (169, 170, 167) or iron overload (167), inhibits the influx of iron into plasma, retaining it in macrophage cells (168).

Would there be a lower secretion of hepcidin in patients with cancer? Low levels of the hormone increase duodenal iron absorption and cause greater release of the metal from the reticuloendothelial system into the circulation (167, 168). And this would occur in subjects with a predisposition to cancer, unlike those who first suffer coronary disease and severe atherosclerosis, who would have higher iron concentrations in macrophages: excessive chronic levels of hepcidin would be a risk marker for heart disease (170).This is corroborated with hereditary hemochromatosis, where the greatest neoplastic pathology due to iron overload is NOT accompanied by coronary artery disease; probably because hepcidin expression (in liver) is inappropriately low (167).

Iron: The Metal that Accumulates progressively and Generates Disease.

Free iron produces a disturbance in zinc metabolism, with proven anticarcinogenic activity and signaling; and particularly in women, alcohol significantly contributes to the increased release of oxidative catalytic iron from ferritin stores (132).

No metal accumulates to such a degree and so quickly as iron; and the metal is a clear substrate for enzymes that directly participate in cell proliferation (171), in addition to its direct effect as a promoter and initiator of cancer (see above); in particular in women with endometriosis, and in men with viral hepatitis, where chronically persistent and continuously increasing inflammation is the best breeding ground for the "eternal" survival of the tumor cell: iron overload creates an environment hyper-inflammatory that powerfully stimulates angiogenesis and tumor cell overgrowth, migration, and invasion, independently of sex steroids (172); and, as we pointed out above, the metal induces the activation of various anti-apoptotic signals – including that of insulin, and that of the nuclear transcription factor NFkB.

Hepatomegaly found in genetic iron overload, such as Hemochromatosis, is reversed with phlebotomy; and although exogenous iron overload in rodents does not induce immediate expression of proliferative genes in insulin-sensitive livers, it does clearly modulate TNF-x expression by Kuffer cells (58; 20, 44): hepatocyte proliferation (rodents) is a consequence of a high iron diet, and is due to the over-stimulation of the cell cycle induced by the increase in Cyclin D1 levels (58,59).

Thus, iron is a direct mitogen, just as lead nitrate is in hepatocytes; Furthermore, hepatic overload (and probably dietary iron) stimulates a greater secretion of TNF-x (58) and the consequent tissue inflammation (resistance to hepatic insulin).

In an extremely interesting report, an increase in hepatic cholesterol secretion due to elevated iron has recently been demonstrated in mice (173).

Biological evidence proves that ferric iron plays a crucial role in the initiation of cancer in non-transformed cells, or in the early promotion of neoplasia in intestinal adenomatous cells (174); this demonstrates, once again, the genotoxic role of iron (10, 174).

Recently, also in prostate cancer, a high transferrin saturation (greater than 30%) has been evidenced, but above all, greater ferritin deposits (175). A case- control cohort (CARET Study) has shown that diets high in iron significantly increased the risk of clinically aggressive prostate cancer (176); and iron caused greater cancer aggressiveness in men with low intakes of dietary antioxidants (fruits and vegetables).

Diabetes and Cancer: The Killer Brokerage of Iron

All patients with adult-onset diabetes are at increased risk of cancer (177); and the inverse seems to be confirmed in the case of the pancreatic tumor. Thus, in general,

there are more and more occult hyperglycemias in subjects with initial or progressive cancer.

There is a complex, direct, and underestimated association between diabetes and increased risk of cancer initiation, progression, and mortality (177); and this reciprocal interrelationship may be closer considering that type 2 diabetes is a commonly NOT diagnosed disease (178) due to compensatory hyperinsulinemia, which turns it into hidden diabetes, with “normal” glycemia. We are sure that this is highly relevant in the case of prostate carcinoma, which is the only one whose overall risk does not seem to increase with the presence of overt diabetes.

Let us remember that hyperinsulinemia significantly favors the development of malignant neoplasms because it is a clear and complex growth factor with multiple mitogenic effects; both at the receptor and post-receptor level (177).

Recently, the EPIC-Norfolk prospective study has clinically demonstrated the prediction of (new-onset) diabetes with elevated serum ferritin levels (179); Thus, as we said before, but now in healthy women, the greater the body's ferritin stores, the greater the risk of suffering from the disease (180). And excessive bodily ferritin is the link between diabetes, obesity (especially android-abdominal) and cancer.

It must be emphasized that iron by itself is capable of initiating disease in humans (181, 182), such as lung cancer (181, 71), and primary osteoporosis - iron increases osteoclastic activity and bone resorption - (183).

Several epidemiological studies have reported a positive association between high iron body stores and increased risk of type 2 diabetes and other insulin resistance states, from metabolic syndrome and polycystic ovary disease to gestational diabetes (102); all of them with a higher incidence of cancer; and it is that a higher oral intake of heme iron increases the risk of DM2 in healthy populations (102, 180) due to drastically raising hyperinsulinemia and tissue resistance to insulin (particularly at adipose, hepatic and muscular levels). By raising insulin, but, most importantly, directly, free iron (not bound to transferrin) amplifies the action of cancer genes (beta-catenin) and promotes the deletion of genes (1) protectors and inhibitors of malignant neoplasms such as the P-53 protein (139).

Categorically, diabetes-associated hyperinsulinemia not only promotes but potentially causes carcinoma (184), particularly in the breast, colon, liver, and endometrium (185,186) through its powerful cell survival signaling.PI3K/Akt; which, when inhibited, has been shown to regress breast cancer (187);however, despite the increasing evidence on the promotion and progression of cancer from diabetes (188) -and independently- (185), the greater the compensatory chronic hyperinsulinemia of resistance to insulin, higher cancer risk, and in the absence of diabetes (186); Thus, by reducing tumor anti-apoptotic insulin signaling (PI3K/Akt), tumor growth is reduced, but hidden hyperglycemia (187) is evident. And this is because, as long as iron stores (and inflammatory catalytic free iron) remain high, glucose intolerance will not disappear, nor will neoplasia be eradicated, since the high permanence of ROS will maintain the oncogenic phenotype. of cancer cells (189).

Hypercaloric Nutrition, Hyperglycemia and Cancer: The Evil Help of Iron

Caloric restriction without malnutrition has been shown to reduce the incidence of cancer in animals and has been done in humans (190) (pre- menopausal women reduce the risk of post-menopausal breast carcinoma); there is growing evidence that lowering IGF-1 (and insulin) levels mediate many of the antiproliferative, proapoptotic, and anticancer effects of caloric restriction; and that restoration of IGF-1 levels reverses the antitumor effects of calorie restriction (190).

Aside from its cell cycle regulatory actions, IGF-1 potently increases cellular iron accumulation by elevating transferrin receptors (191), a protein that itself stimulates DNA replication in the neoplastic cell (192). And IGF-1 in isolation, although it has powerful oncogenic power, is not capable of promoting cancer growth: the presence of transferrin is necessary for the proliferation of human myeloblastic leukemia cells (193). In addition, free iron is a potent survival factor for myeloid cells (194); and its evil transformation (see above).

The accumulation of adipose tissue induced by a hypercaloric diet (195) with or without visible obesity, produces high proportions of reactive oxygen species (ROS), inflammatory cytokines (91, 125), angiotensinogen and the chemotactic protein MCP-1, powerfully reducing genome stability (195); We believe that this is due to the higher content and tissue uptake of iron dependent on adipose resistance to insulin.

Glucose intolerance is an independent factor that increases cancer mortality in the general population, according to an extensive study conducted in the USA (Second National Health and Nutrition Examination Survey and the Second National Health and Nutrition Examination Survey Mortality Study) (196); in such a way that chronic hyperinsulinemia would confer a higher predictive risk of cancer mortality than diabetes "per se", due preciselyletovethlsewfaocutldthbaet hmigohrer insulin powerful for the induction of cancer than hidden hyperglycemia (post-prandial).) (As occurs in prostate cancer, not associated with obvious diabetes) (197).

However, the opposite occurs in relation to the pancreas: since the high exogenous supply of heme iron (198) confers a greater risk for diabetes (especially to the woman), it is indirectly explained that postprandial hyperglycemia increases the risk for pancreatic cancer (199); mainly in males; pancreatic carcinoma could mean the final stage of iron-dependent “borderline” diabetes.

Hyperglycemia is common among cancer subjects; both high intakes of sugars and refined carbohydrates (200) and high blood glucose levels (200, 201) are strongly associated with increased cancer risk; being able to determine its mortality: there is clinical evidence that indicates that a high carbohydrate diet is associated with poor survival (post-diagnosis) of early breast cancer (200).

Hyperglycemia is a prominent feature of overnutrition (201), as is excess body iron; and epidemiological evidence supports the fact that high blood glucose levels –even in the non-diabetic range- are an independent risk factor for developing cancer (201).

Today it is known that acute glycemic excursions increase the activation of the anti-apoptotic nuclear factor NFkB (27) in healthy thin adult mononuclear cells (202); just as iron does in macrophages (20); and thus, by activating the main factor associated with the initiation and promotion of cancer (203), whose signaling is strongly anti-apoptotic (27) in addition to activating numerous chronic and promutagenic (10) inflammatory (203) cascades. It is necessary to emphasize here that, even in normal young thin subjects, normal-elevated physiologic increases in postprandial glucose are inflammatory (202).

Today, early detection and therapeutic correction of chronic insulin excess is necessary and urgent, especially in women, which will substantially help reduce morbidity and mortality from total cancer (195), and particularly breast cancer. (184, 204). The crucial role of iron in the generation of hyperinsulinemia; and directly in the generation of human cancer of hormonal etiology, must be urgently prevented today by reducing the carcinogenic accumulation of the metal (164, 22).

The quintessential antidiabetic, Metformin, by reducing chronic hyperinsulinemia, improving insulin resistance at the liver, adipose, and muscle levels, is demonstrating a powerful anticancer effect (205, 206, 207). This anticancer action could be due, initially, to the reduction in iron absorption, which has been widely suggested to significantly improve insulin resistance in women with polycystic ovaries (208): this syndrome, even subclinical (with the presence of ovulations) has high incidences of breast cancer; confirming that the chronic excess of insulin (120) powerfully increased by iron, would be the underlying cause of breast cancer.

Body Iron Reduction: The Most Effective Therapy to Reduce Disease.

Iron-depleting therapy can reduce fibrosis and liver cancer (209), symptomatic and hemodynamically decompensated atherosclerosis (210), and arthritis. gouty (211); and all this, especially because insulin sensitivity is improved: even in non-pathological conditions, reducing accumulated body iron reduces insulin resistance (31), which, as we pointed out before, is a clear -but underestimated- predictor of disease (34).

Recently, the first case of complete remission of a severe case of chemo-resistant acute monocytic leukemia has been reported with Deferasirox, a powerful iron chelator (212), similar to the improvement that iron depletion promotes in many childhood leukemia cases (see above); thus, the new pharmacological agents that capture free iron become powerful antiproliferative agents (213) in cancer, even advanced.

Corroborating the mutagenic and neoplastic effects of iron, the most obvious and powerful known exogenous carcinogen, Asbestos, is proportional to the concentration of iron content (214).

The measurement of body iron stores, measured as serum ferritin, is a risk factor for cerebrovascular accidents (Stroke) according to a large cohort study with more than 11,000 postmenopausal patients (215), due to increasing thrombogenesis and thrombogenesis by various mechanisms. vascular inflammation (see above).

In addition, more evidence is accumulating that iron plays a crucial role in the promotion of neurodegenerative diseases, particularly Parkinson's disease: intranasal iron injections selectively damage dopaminergic neurons (216); while metal restriction powerfully protects against induced parkinsonism (217).

Hemoglobin is a potent neurotoxin that significantly contributes to neuronal death following trauma or intracranial hemorrhage (218); and its neurotoxicity is substantially mitigated by iron chelation by apotransferrin (219). And, the greater the amount of Ferritin, the greater the risk of suffering a cerebrovascular accident in post-menopausal women (215).

Elevated Free and Accumulated Iron: A Risk for the Promotion and Spread of Disease.

The recently discovered Ndrg-1 metastasis suppressor gene is negatively regulated by iron (220); The greater the iron ingested and accumulated, theoretically, the greater the metastatic power of cancer (see later).Changes in iron regulation characterize the cellular state of malignancy (123): Free iron induces, mediates, and increases oxidative stress (10, 221).

Exogenous iron is capable of modifying the four bases of renal chromatin only 24 hours after its administration (10), demonstrating its damage to DNA in vivo; and although it is true that it can intervene at the same time in its repair, it is insufficient to prevent genotoxic aggression (222); however, beta-carotene-for example- it is capable of completely preventing the intense lipid oxidative damage to iron-induced prostate tissue (221).

Very interesting, the DNA damage caused by Retinol is inhibited by iron neutralizers (Scavengers), which indicates that retinol-induced DNA damage is associated with a regulation of iron turnover; thus, accumulated iron is co-responsible for the high incidence of lung cancer associated with retinoid supplementation (223).

Cancer subjects who consume more calories, regardless of their adiposity, will have a worse prognosis, perpetuating a chronic excess of insulin (184, 187, 195) (and other inflammatory hormones, such as leptin, sex steroids, etc.) ; and thus increase vascularization (angiogenesis) and the capacity for tumor metastasis, through the increase and activation of VEGF (vasculo-endothelial-growth- factor) by insulin (224).In this way, ROS reactive oxygen species -powerfully increased by iron- amplify cancer growth (insulin-dependent), and its distant spread (VEGF-dependent).

Oral iron overload, in addition to not improving malnutrition, on the contrary increase's resistance to tuberculosis (225), as has been the case for decades in Africa, since it increases aggressiveness and bacterial replication. Dietary iron is clearly associated with a high incidence of disease (226), in addition to promoting its worsening, by

increasing any pre-existing inflammation: cellular iron behaves as a pro-inflammatory agent, and its high tissue levels contribute decisively to the disease pathogenesis (69). There is enormous and accumulating evidence that excessive dietary iron is both an initiator and a promoter of disease (121, 226).A high transferrin saturation increases the risk of general mortality; and this has been verified in the 12-year cohort study (The second National Health and Nutrition Examination Survey 1976–1980 -NHANES II- and the NHANES II Mortality Study 1992): A high iron intake in subjects with high transferrin saturation significantly increases the overall risk of dying (227).

On the other hand, in any pathophysiological state where there is a decrease in serum Transferrin, such as hyperglycemia or gestational diabetes, iron loads are gastro-damaging (228), and, what is more serious, potentially teratogenic (229). . Let us remember that pregnancy is a state of physiological insulin resistance that is frankly pathological in women with previous android obesity (230).

Non-enzymatic glycation –induced by hyperglycemia- significantly increases oxidative stress in the presence of iron (95); Thus, reducing the contribution of the metal in gestational diabetes prevents fetal malformations (228). Clearly, numerous clinical studies demonstrate that those with gestational diabetes, occult diabetes, or pre-eclampsia should not receive iron supplements in the first half of pregnancy (231): multiple evidence indicate that Elevated iron during human gestational organogenesis is potentially teratogenic (229).

Free iron is toxic to cellular systems (232) and must be immediately neutralized and captured by ferritin (intra and extracellular) so that it does not cause, increase, or perpetuate inflammatory cascades, a critical event for tumor formation and progression. (67). Furthermore: in the presence of the current diet, which is clearly acidogenic (233), free iron is released much faster: all iron-dependent lipid peroxidation processes are enhanced when the extracellular pH is acidified, as greater amounts of iron are released (234) from protective sites, such as ferritin (232).

Furthermore, if dietary iron loads were not, as inflammatory, eg. a decade ago, now they are more and more so: in the presence of saturated fat, its mutagenic damage is potentiated, by increasing the passage of iron to the mitochondria, and its consequent chromosomal injury (235). And the greater amount of free iron in the mitochondria induces alteration of its energetic homeostasis; and the compromise of mitochondrial energy generates genomic instability and the potential appearance of cancer (236).

In other words, the integrity of the nuclear genome and its mutability depend first of all on mitochondrial function (236), and it depends on intracellular iron levels (237). It is noteworthy that nuclear genetic mutations by themselves do not cause cancer; and that mitochondria and their metabolic environment play a dynamic role in the regulation of carcinogenesis (epigenetic metabolic regulation) (236).

In accordance with the above, the reduction of permanent inflammation (induced by viruses, radiation or iron) is crucial to prevent the development of cancer. (67,203, 236). A 24-year study conducted in the USA among the white population shows that higher dietary intake of iron is directly correlated with ten types of cancer (238) (bladder, breast, colon, esophagus, stomach, rectum, and Hodgkin lymphoma). Very interestingly, these same neoplasms were associated with a low zinc nutritional index (238); and the tissue availability of zinc is reduced by the high intake of

dietary iron (239); thus, excessive iron also indirectly increases the risk of cancer by reducing the DNA repair, antioxidant, and antineoplastic effects of zinc (238).Iron excess causes deletion of the guardian gene of the CDKN2A/2B genome, (generator of the ARF tumor suppression gene), as recently demonstrated by Toyokuni (240); Iron compounds by themselves generate malignant mesothelioma, through the affectation of this gene.

Currently, phlebotomy in conjunction with a low-iron diet is the second line of therapy for the prevention of hepatocellular carcinoma in Japan (81). The lower the body's iron stores, the lower the incidence of cancer in humans (75); Thus, in 2008, it has been shown that reductions in body iron by phlebotomy reduce the risk of visceral cancer by 35% and decrease mortality by 60% in subjects who are not pathologically overloaded iron (42). Free iron increases the invasiveness and distant metastases of invasive cancer by increasing the expression of the metalloproteinase MMP-9 (241).

In addition to slowly and progressively increasing any subclinical inflammatory pathology, excessive iron is today considered a powerful initiator of liver (40) and cardiac (242) damage: iron is crucial in the physiopathogenesis of liver fibrosis as well as in liver injury. acute; and vice versa: a diet deficient in iron effectively reduces liver damage, in models of acute and chronic injury (40). In fact, it should not surprise us that elevated tissue iron causes apoptosis and cardiac fibrosis (242), since it does so also, and much more readily, in liver cells (see above).Consistent with all the evidence already mentioned, it has recently been shown that an acute increase in free iron causes structural remodeling of the pulmonary endothelium, as a result of causing a cellular proinflammatory phenomenon (243).

Even in the presence of a low exogenous supply, ideally, iron should be used, distributed, eliminated and not accumulated in excess, so that it is not harmful and promotes disease: the problem, added to the almost null physiological elimination (1), it is that the metal is not adequately distributed in the presence of systemic or hepatic inflammation, being accumulated in macrophages and tissues; which is evident in chronic anemia, where the oral contribution of exogenous iron does not solve the inflammatory or infectious problem that causes it (69).

Chronic anemia can be protective (69) against the accumulated excess of iron due to previous infection and/or chronic inflammation. Thus, in the face of any degree of hepatic steatosis (or much worse of aggression to the hepatocyte) there will be no good redistribution of iron, due to the alteration of the secretion of the iron-regulating hormone Hepcidin (240), which will increase and sequester the iron Ferroportin complex, preventing it from passing into circulation (see above).

High exogenous iron loads, in a dose-dependent manner, cause programmed cell death of cardiac, hepatic, and pancreatic cells (244). Furthermore: even at “normal” levels, iron has deleterious effects on the function of pancreatic beta cells (90); and at high doses in its structure (244); pancreatic function is reversible with dietary restriction (90).

Large and growing epidemiological, experimental, and, to date, clinical studies prove a very close relationship between carcinogenesis and exogenous iron overload: regular semi-annual phlebotomies continue to be reported to reduce the risk of cancer even in normal populations (240); and the extraction of accumulated iron is much more

urgent in those subjects with genetic hemochromatosis, chronic viral hepatitis, ovarian endometriosis, and asbestosis -all pathologies that inducelegareda, treersiproenctoivveelyrl,otaod- and that hepatocellular and ovarian carcinoma or human mesothelioma patented, for example. in diabetic women, who, despite having more anemia than their male counterparts, accumulate more iron in their retinas (245). In this regard, the toxicity of elevated iron on the retina has been fully demonstrated (246, 245), especially in the diabetic population (245). We must emphasize that chronic anemia due to advanced cancer is not solved by providing oral iron, since its cause, as in any chronic anemia, is due to the overproduction of Hepcidin (1), the hormone that pathologically reduces duodenal absorption, and favors tissue and hepatic retention of iron (see above). If we do not treat the cause first, we run the risk of worsening the prognosis of the pathology: e.g. It has been shown that, in a dose-dependent manner, the greater the transfusion of red blood cells, the greater the risk of postoperative infections (247, 248, 249): the greater bioavailability of iron increases viral and bacterial replication, increasing its virulence and aggressiveness; and it is that excess iron -or its largest deposits such as ferritin- increase susceptibility to infections (250) because iron is the fundamental nutrient for the growth of germs,in addition to cancer cells; In this regard, new clinical and epidemiological evidence stands out that dietary iron participates in the pathogenesis of esophageal, stomach (251) and lung (252, 253) cancer. In a prospective study that covered 7 years and more than 400,000 subjects of both sexes, it was evidenced that the minerals ingested in the diet are a risk factor for lung cancer (253); and there is growing evidence that dysregulation of iron metabolism, and especially of its free fraction, is the primary cause of neurodegenerative pathology (254, 255).

In addition, as we pointed out before, each cell needs iron to proliferate and grow, and with much greater avidity, this occurs with the neoplastic cell: thus, an environment rich in iron facilitates and promotes tumor growth, and the amount of synthesized DNA increases. in the presence of metal; as occurs with the hepatitis B virus, which activates its replication and increases its ability to infect due to the increase in tissue ferritin (77). Therefore, the greater availability of exogenous iron is capable of markedly enhancing infectivity and viral replication.

Severe deficiency, but particularly iron overload, is clearly thrombogenic (152), inflammatory (150, 153), 155) and cytotoxic, promoting retinal (256, 257, 258) and lens cell degeneration (258), and of neurons (255, 254). And, in the presence of significant insulin resistance, such as Pregnancy Hypertension, exogenous iron supplements are profoundly deleterious (259), Pre-Eclampsia being a potential prediabetic state (230); profoundly exacerbating endothelial dysfunction, by increasing tissue resistance (vascular, hepatic and adipose) to insulin.

Clinically, in a population without genetic risk markers, excess free tissue iron will favor first (and early) the appearance of Diabetes Mellitus (260, 102,103, 90, 115), contributing clinically and histologically to its complications (106). Then it will lead us more easily to cancer. If, as has been shown in an interesting pilot study, only 4 months of a high iron diet (“high normal”) are enough for the childhood development of Diabetes 1 (260); time will be increasingly "shorter" for the appearance of degenerative diseases and cancer.The pathology of iron accumulation, which is currently growing due to uncontrolled contributions of free iron in the diet (93, 226, 174), is very insidious: today, iron constitutes a "quiescent time bomb" (240).

Today, the basic sciences reveal to us that the diseases of aging overlap -heart disease, diabetes, degenerative diseases (oculo-neurodegenerative) and cancer-; and that in all of them, the tissue deposit of iron (257, 255, 90), and insulin resistance is very evident (34); therefore, dietary iron, increasingly dangerous in the context of current "nutrition" (235, 234, 236) is powerfully carcinogenic, aggravating its morbidity and mortality; and, additionally, and a potential contributor to neurodegeneration (261, 216, 254, 255). Supplemental iron in humans is clearly genotoxic (159, 334, 511, rev, 512).

Appendix

To be continued in Iron in Initiation and Promotion of Human Cancer -How Free Iron Accelerates Predisposing Insulin Resistance **(Research project part 2)**