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COVID-19 and Body Iron: A Survey on Phenomenological and Genetic Correlations

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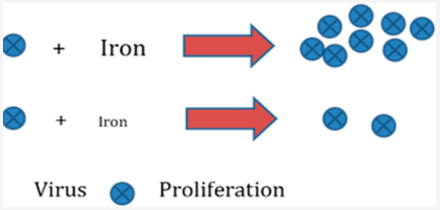
ABSTRACT: To provide solid information about viral infection, disease, and body iron metabolism, the literature was surveyed for mutual correlations. Gender and age profiles of COVID-19 infection and disease correlate well with the profiles of serum iron and ferritin with correlation coefficients ≥ 0.75. There are further symptomatic hints that the ABO blood group system contributes to these correlations. Remarkably, the susceptibility to both the viral disease and iron dyshomeostasis can be traced back to the same gene loci of the ABO blood group system. The overlapping of susceptible gene loci together with the phenomenological correlations in gender and age are strong indicators for the interrelation of body iron dyshomeostasis with COVID-19 infection and disease.



KEYWORDS: *Iron metabolism, COVID-19, phenomena, gene loci*

BODY IRON

Iron has played a fundamental role in life on earth from early iron−sulfur clusters to modern oxygen iron chemistry. Iron is now involved in many electron transport and oxygen binding reactions. Body iron varies between about 60 and 70 mg/kg body weight with the lower values typical for women and the higher for men. About two-thirds of the iron is bound in hemoglobin, a fifth in storage proteins like ferritin, a tenth in myoglobin for muscle work, and the remainder in functional iron enzymes and transferrin, the iron transporter in blood.

Two ionic forms are physiologically relevant. They can be interchanged through the redox reaction $Fe^{2+} = Fe^{3+} + e^-$, which further can lead, via the Fenton reaction, to toxic reactive oxygen species (ROS). The ferrous form (Fe^{2+}) is soluble in neutral aqueous solution, but the ferric form (Fe^{3+}) dissolves exclusively at acidic pH. Both ions are bound to proteins either as porphyrin complex (e.g., in hemoglobin as Fe^{2+} (where the binding of oxygen induces a spin change)) or as Fe^{3+} coordinated to proteins. Maybe because nature could not construct gates for trivalent cations, intracellular or luminal Fe^{3+} must first be reduced to Fe^{2+} to pass through membrane transporters.

Iron is taken up in the intestine from food. A specific excretion pathway of iron is not known, but it is lost by bleeding (mostly by female menstruation) and desquamation. Since iron homeostasis is essential, iron uptake and storage are finely balanced. If iron homeostasis is lost, a number of diseases can result. Low iron concentrations can lead to anemia and high iron to iron storage diseases and in the severe case of iron overload to hemochromatosis. Low body iron levels can be treated by iron substitution in the diet and high iron levels by iron chelating agents, such as deferoxamine (Desferal), used as an antidote against metal ion intoxication.

Over the last number of years several diseases have been correlated with high body serum iron concentrations. When brain iron levels increase, neurodegenerative diseases (e.g., AD, PD) can be affected.[1] Iron depositions in the brain have been visualized by MRI for more than 25 years.[2] Iron is needed for tumor growth[3] and for the proliferation of bacteria and viruses.[4] Because of the importance of these interactions a new term: ferroptosis (from ferrum (lat. iron) and apoptosis) has been coined for iron induced cell death.[5]

The small protein hepcidin is the major player in iron metabolism. Under inflammatory conditions, it is upregulated and binds to ferroportin, thus closing the gate for iron export from epithelial cells and macrophages, which leads to a reduction of blood or serum iron (inflammatory anemia).[6] Conversely, a down regulation of hepcidin leads to the opening of the ferroportin gates.[6]

Serum iron circulates in serum in the bloodstream. It is Fe^{3+} chelated to transferrin (about 90%) or iron in the ferritin complex (10%). Transferrin can maximally bind two Fe^{3+} ions, while the ferritin protein complex can store up to 4500 Fe^{3+} ions in the form of Fe^{3+}-oxyhydroxy complexes. The vast majority of ferritin is found intracellularly in the liver, spleen, and bone marrow. Ferritin is a form of depot iron. The small amount of serum ferritin is considered as an indicator of iron storage functionality. Typically serum iron and ferritin concentrations

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are measured in laboratory blood tests. A third parameter measured is the total iron binding capacity (of transferrin).

The following survey focuses on serum iron and serum ferritin as the status of the iron metabolism. In all diseases where iron contributes, it is open for discussion whether the iron status is the cause or the consequence of subsequent reactions.

COVID-19

Infection and Disease. COVID-19 is a new infection by the SARS-CoV-2 virus. The infection started in the Chinese city Wuhan at the end of 2019 and rapidly spread over the whole world, principally via viral transfer by exhaled air of infected persons. From the initial throat and nose infection, the virus reaches the respiratory tract and the lungs where it proliferates and can lead to severe disease outcomes, including death. Whether and how the infection is transferred into the blood or lymph stream and further distributed over body organs possibly also crossing the blood−brain barrier is the subject of major and intensive clinical studies (see, e.g., Baig et al.[7]). As a case in point, the infection of the Spanish Influenza virus in 1920 was much later discussed as a possible origin for the "infectious" Parkinson's disease (PD).[8] (Heinz Lawaczeck (1891−1963) always communicated since he developed Parkinson's disease at the beginning of 1950s, that his own and the Parkinson's disease of his patients were results of an infection by the Spanish influenza virus about 30 years earlier.) Evidence suggests that SARS-CoV-2 binds to ACE2 (the angiotensin converting enzyme 2 present in lung alveolar cells, in the heart, and in other organs) and is internalized with the help of the enzyme TMPRSS2 (a transmembrane spanning serine protease).[9,10] The role of the organ distribution of the ACE2 receptor in COVID-19 pathophysiology is extensively discussed by Bourgonje et al.[11]

ABO Blood Groups. Very recently a phenomenological correlation between human ABO blood groups and COVID-19 infection and severity has emerged (so far as a preprint). This comparative study[12] is further supported by the study on gene loci of susceptibilities for COVID-19[13] (see below).

Gene Loci for COVID-19 Susceptibility. In a large and elaborate study, the genetic fingerprints on the severity of COVID-19 infections have been studied by analyzing more than eight million single-nucleotide polymorphisms (SNPs) of hospitalized COVID-19 patients in Italy and Spain during the early days of the pandemic in spring of 2020.[13] Seven loci showed SNPs related to the COVID-19. These and the functions, they code for [see ncbi.nlm.nih.gov/gene], are as follows:

SLC6A20: Membrane transporter of small hydrophilic molecules like ions; multiple isoforms, absorption and secretion from/to intestine
LZTFL1: Transcription factor
CCR9: Beta chemokine receptor family
CXCR6: C-X-C chemokine receptor type 6
XCR1: Subfamily of chemokine receptors
FYCO1: Directed transport of autophagic vesicles
ABO: Determines the ABO blood group

With the exception of the ABO blood group locus on chromosome 9, the other gene susceptibilities are located on chromosome 3. The presence of the ABO blood group dependence supports the results of Zhao et al.[12] The three chemokine receptors (CCR9, CXCR6, and XCR1) refer to a strong focus on inflammatory reactions.[14]

IRON AND COVID-19

Phenomenological Correlations: Gender and Age Differences. Early in the course of COVID-19, a gender difference was noted with a male/female mortality ratio of 75:25.[15] For the viral cellular uptake system, ACE2, it was found that the soluble part of this enzyme shows higher blood plasma concentrations in men than in women.[16,17] This gender difference in soluble ACE2 was then associated with the gender difference in infection and severity of the viral disease. However, the gender difference observed can also be related to the lower serum iron content of women during their reproductive ages compared to men.

The age and gender distributions of serum iron concentrations correlate well with the susceptibility of COVID-19. As shown in Figures 1 and 2, serum iron and serum ferritin for

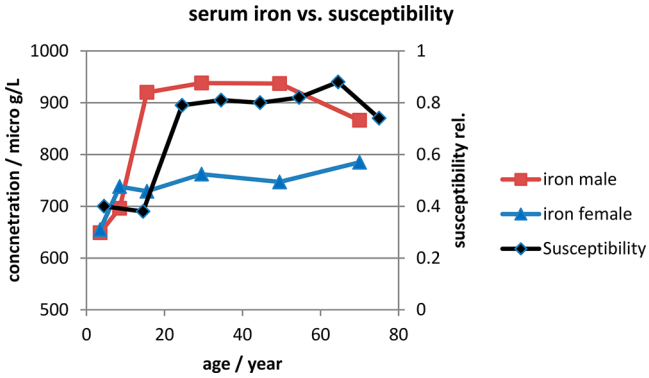

Figure 1. COVID-19 disease susceptibility (right scale) and serum iron concentrations in a normal U.S. population (left scale) as a function of age and gender.

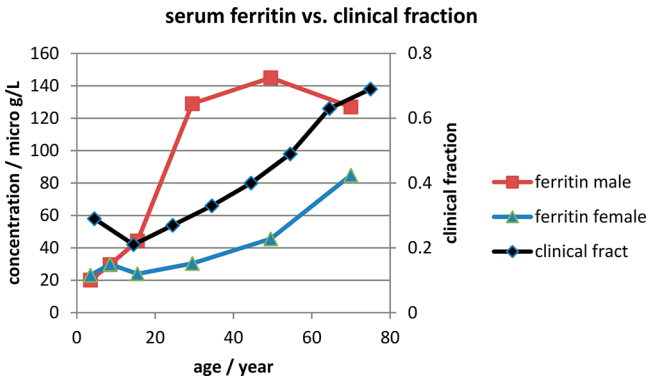

Figure 2. COVID-19 disease clinical fraction (right scale) and serum ferritin concentrations in a normal U.S. population (left scale) as a function of age and gender.

children and young adults are low during their growth period. The serum iron and serum ferritin concentrations for women from adolescence to menopause are considerably lower than serum iron values for men, due to menstruation and thus loss of iron. Post menopause, the concentrations for men and women converge.

Data for COVID-19 from Davies et al.[29] and iron data from the National Report[30] point to quantitative differences of serum iron and ferritin values between Mexican-American, African-American, and White U.S. citizens. At the same time, the forms of profiles are unchanged and resemble those of Figures 1 and 2.

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The concentrations of soluble ACE2 for boys and girls as a function of age diverge like a pair of scissors from 8 to 24 years[17] in a similar manner as seen for the iron values in Figures 1 and 2. In both cases, boys show larger values compared to girls.

The visual trends in Figures 1 and 2 were further quantified by calculating correlation coefficients P_{cor} between the iron related and the disease related data. The results are summarized in Table 1.

Table 1. Correlation Coefficients P_{cor} between the Data for Serum Iron Male (SIM), Serum Iron Female (SIF), Serum Ferritin Iron Male (FIM), and Serum Ferritin Iron Female (FIF) Correlated with the Corona Susceptibility and Corona Clinical Fraction from Figures 1 and 2[a]

	SIM	SIF	FIM	FIF
susc	*0.76*	0.65	*0.99*	*0.75*
clinic	0.34	0.24	0.73	*0.92*

[a]Values $P_{cor} \geq 0.75$ are shown in italic.

Table reveals a strong correlation ($P_{cor} \geq 0.75$) between serum iron in men and a high degree of correlation ($P_{cor} \geq 0.5$) for the same correlation in women. The serum iron levels have almost no influence on the course of the disease in contrast to the ferritin values which act both on the susceptibility and the outcome of the disease (clinical fraction). An even more robust correlation might be expected if gender specific disease parameters were available and the data sets were not combined from different cohorts but from one study. However, the trends of the iron values (pre infection) from different cohorts are all similar.

ABO Blood Groups. Hints from the literature[18,19] support a correlation between iron levels and blood groups, but apart for studies on multiple blood donors the literature is poor. There might also be continental diversities.

Concerning COVID-19, the work of Zhao et al.[12] suggests a gender and age relationship, with an increase in disease burden with age from below 40 years to above 60 years and a lower burden for women compared to men.

The serum iron values reflect the gender difference and show a decrease in iron values in the order A > B > AB,[18,19] which parallels the observation of Zhao et al.[12] on COVID-19 cases. Disease parameter for blood group O corresponds approximately to vales for blood group B.[12] Zhao et al. speculate that natural antiblood group antibodies might induce the observed effects, however, more work is needed. In the discussion of the ABO blood group loci, Ellinghaus et al.[13] refer to the von Willebrand factor which plays a major role in hemostasis and also shows an overlapping of susceptibility gene loci with the ABO system.[20]

COVID-19 AND HEMOCHROMATOSIS SUSCEPTIBILITY GENE LOCI

Overlapping in ABO. In order to find out whether gene loci relevant for iron dyshomeostasis overlap with those gene loci considered above, a comparison with iron relevant gene loci was performed. As a substitute for patients with iron dyshomeostasis, patients with hemochromatosis were compared with the severe COVID-19 GWAS groups.[13] For patients with hemochromatosis, genetic association data has been published.[21] The hemochromatosis susceptible gene loci are distributed over a number of chromosomes and refer to iron marker and iron metabolism. The following genes are affected:

HFE: High iron in hereditary hemochromatosis

SLC40A1: Iron transporter ferroportin

TF, TFR2, TFRC: All three related to transferrin (TF) or TF receptor

TMPRSS6: Transmembrane spanning serine protease identified above; enzyme TMPRSS2[9,10] Helps the coronavirus to get internalized

ABO: Determines the human blood groups on chromosome 9

ARNTL: Aryl hydrocarbon receptor nuclear translocator like

FADS2: Acyl-CoA 6-desaturase

NAT2: *N*-Acetyltransferase 2

TEX14: Testis-expressed gene 14

The first six loci include known iron related genes. The last five entries have not been previously correlated with iron homeostasis; they refer to transferrin and ferritin.[21]

It is immediately evident that SNPs in the ABO blood group loci at chromosome 9 appear both in the COVID-19 and hemochromatosis study groups. Furthermore, SLC40A1 from the hemochromatosis group codes for ferroportin, a transporter for divalent iron ions leading the intracellular iron into the blood lumen. SLC6A20 from the COVID-19 group is a carrier for small hydrophilic molecules across cell membranes and could possibly also be associated with iron ions (Fe^{2+}) trafficking. The other risk gene loci and their mutual interrelation should be discussed further at another time.

THE CORRELATION BETWEEN COVID-19 AND BODY IRON

The clear overlap of the gene loci for the ABO blood group system in both the COVID-19 susceptibility genes and the loci for the iron functions reveals a direct correlation on the genetic basis that strongly supports an influence of body iron on the infection and burden of the viral infection. The involvement of the chemokine coding loci of the COVID-19 group points to inflammatory reactions where especially the values of serum ferritin can reach extremely high values, an effect called hyperferritinemia.[22] This induced ferritin storm can become an indicator for severe inflammation as has been pointed out recently with respect to mortality with mean values of 614 μg/L in the survival group and 1298 μg/L in the nonsurvival group.[23] Liu et al.[24] reported ferritin values of 268 μg/L for patients with mild symptoms and 836 μg/L for patients with severe symptoms. For comparison, the author of this Perspective, R.L., during 2019, had a mean value of serum ferritin of 87 ± 33 μg/L and a corresponding serum iron level of 1060 ± 370 μg/L. Why the observed inflammatory storms go together with hyperferritinemia must be studied in greater detail. Under "normal" inflammation, hepcidin is upregulated and it binds to ferroportin, closing the iron gates so that the intracellular iron pool is withheld from release into the blood lumen.[4,6] The blockage of ferroportin decreases the iron absorption from the intestine and thus also reduces the amount of available iron for hemoglobin charging.

In a comprehensive systematic review and meta-analyses, including data up to the beginning of August 2020,[25] it was observed that the hemoglobin values decrease with the severity of the disease and at the same time serum ferritin levels increase,

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as discussed above, leading to anemic conditions (serum iron values are not available).

Serum iron values of a Wuhan group of 50 patients in parallel with the course of the disease were recently studied.[26] Pretreatment serum iron values for the three hospitalized categories of mild, severe, and critical are similar and around 314 μg/L and thus lower than normal with values between 437 and 1792 μg/L. Post-treatment, the serum iron levels increase and show a decline with severity from 1210 (mild) to 661 (critical) μg/L. These serum iron levels are in the normal range, but are negatively correlated with the progress of the disease.[26] The initially low values can be understood on the basis of the inflammatory anemia leading to a decrease in serum iron mentioned above. In an advanced statistical analysis, the authors demonstrated that post-treatment serum iron levels could predict the mortality of the disease[26] (ferritin values were not reported). The increase of serum iron under therapy might be due to the control of inflammation, which seems to be less effective for the critical patients.

So far, the correlation of iron with SARS-CoV-2 infection and COVID-19 disease justifies further studies at both the bench and the bedside. Accepting the role of iron may open new ways in therapy like the use of iron chelators as recently proposed[27,28] or more specific siderophores. One major limitation results from the fact that, in the correlation of age and gender with body iron, data sets of different cohorts are considered. Compact studies specifically aimed at the understanding of the viral infection and burden with body iron are rare.[26] For prevention, an iron poor or vegetarian diet might be of advantage: low iron means low viral proliferation. Under therapy, both viral load and inflammatory symptoms must be controlled.

Currently, it is open for discussion whether iron acts directly on a biological pathway or on specific targets (being a cause) or whether it paves the way for redox activities in a general sense (being of more consequence). This question which has also been asked by Edeas et al.[22] cannot yet be answered. Both virus and iron must listen like a dancing couple to the beat of the music. The conductor of this scene is so far unknown.

CONCLUSION

The relationship between age and gender and COVID-19 infection and course of disease correlate well with the relationship between age and gender and serum iron and serum ferritin values confirmed by large correlation coefficients ($P_{corr} \geq 0.75$) . There is also evidence for a correlation with the ABO blood groups. In the genetic fingerprints of susceptibilities for COVID-19 and for iron dyshomeostasis, the same ABO gene loci are affected. There might be more overlapping gene loci involved. That has to be studied in greater detail including a possible interrelation between ACE2 and cell iron status. Likewise, the ferritin storm observed in hospitalized patients with severe symptoms should be investigated further.

METHODS

A literature survey is presented. Common factors for COVID-19 and iron metabolism, i.e., serum iron and serum ferritin, were searched and compared, specifically for gender and age profiles. The survey is extended to susceptible gene loci characteristic for COVID-19 and the iron storage disease, hemochromatosis, as a substitute for iron dyshomeostasis.

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Notes

The author declares no competing financial interest.

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