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Review Article

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Significance of Ferritin as Biomarker in SARS Corona virus (Covid-19) infection and complications: A Review

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Abstract Severe Acute Respiratory Syndrome Coronavirus-2 Covid 19 (SARS-CoV-2) suddenly appeared in middle of 2019, spreading in Wuhan province of China, an endemic occurred till Dec 2019. Present review describes the function, regulation, role of Ferritin as inflammatory marker and its significance in several co-morbidities of SARS CoV-2 such as pneumonia, haemophagocytic lymphohistiocytosis, secondary haemophagocytic lymphohistiocytosis, Lymphopenia, cytokine storm or simple bleeding and coagulation disorders.

Keywords Ferritin, Biomarker, SARS Corona virus, Covid-19 infection

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 Covid 19 (SARS-CoV-2) suddenly appeared in middle of 2019, spreading in Wuhan province of China, an endemic occurred till Dec 2019, which then spread to the world causing 1.04 million deaths and 35.7 million active cases as of September 2020 (WHO). Multiple arrays of studies were done, which now stood in thousands, regarding causes, symptoms, signs, treatments, hospitalizations, Intensive Care Units setting, diagnoses modules, diagnostic testing and more importantly biomarkers, that can diagnose and can provide prognosis about severity and progression of Covid 19 infections, pneumonia, organ and systemic dysfunctions, cardiac and neurological abnormalities and untoward inflammatory responses. Several inflammatory biomarkers such as Interleukin 6 (IL6), C-reactive protein (CRP), Cluster Differentiations (CD4+, CD8+), Procalcitonin (PCT), D-Dimer, Ferritin and Lactate dehydrogenase (LDH), have been indentified in last 8 months and now been routinely tested for disease progression, prognosis or to evaluate the effectiveness of treatments. Present review describes the function, regulation, role of Ferritin as inflammatory marker and its significance in several co-morbidities of SARS CoV-2 such as pneumonia, haemophagocytic lymphohistiocytosis, secondary haemophagocytic lymphohistiocytosis, Lymphopenia, cytokine storm or simple bleeding and coagulation disorders.

Discovery, Structure and Function:

Ferritin is an iron storing protein, large, spherical in shape [1, 2]. It was first described in 1930s as an earliest protein to be convoluted in iron metabolism, and as component rich in iron and later purified from horse spleen [1, 2]. Literature acquainted that Ferritin has been conserved all these millions of years through evolution; in addition to becoming an iron deposit, its importance was also mentioned in protecting cells from free iron and facilitating immuno-regulatory functions [3-5]. Ferritin confined to its cytosolic compartment, however it can also be found in other system and organelles, such as nucleus, mitochondria and serum [5-7]. Cytosolic Ferritin is a hollow-cage protein which is 450kDa in molecular weight and can hoard upto 4500 Ferrous atoms. However, ferritin structure

consist of two subunits of 20kDa molecular weight each, H-ferritin (FTH) and L-Ferritin (FTL), with specific functions and concentrations, coded by genes located on 11th and 19th chromosomes, respectively [5,8]. Around three decades ago in 1991, ferroxidase moiety of FTH subunit was notified, which is centered with oxidation of ferrous ion and storing it, in addition to delivery to the cells.

Regulation, Secretion and Degradation

It is documented that regulation levels that occurs post-transcriptionally are basically responsible for iron metabolism and ferritin levels per se [5, 9]. Two important components, Iron responsive elements (IRE) and Iron regulatory protein (IRP) are responsible for the same and interact to manifest desired results. Moreover, ferritionophagy is a process through which amount of intracellular ferritin is degraded, proceeding to regulation and circulation. Several steps follow till end inclusive of autophagic/lysosomal targets, activity of cargo nuclear receptor co-activator 4 and then selectively seeking out ferritin for degradation [9-11]. Tissue necrotic factors is also known to facilitate ferritin present in cytosol, and the process is known as ferroptosis, that involves increasing intracellular iron availability, oxidative stress and lipid per-oxidation [12, 13]. Degenerative diseases like Alzheimer's, Huntington's and Parkinson's in addition to carcinogenesis also showed signs of ferroptosis at different stages.

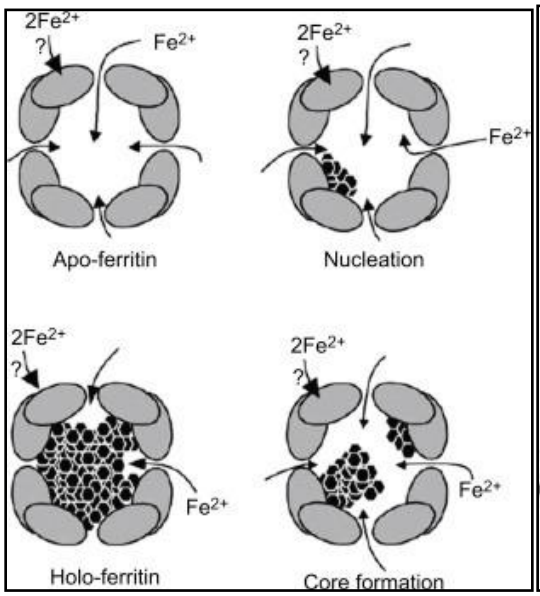

Figure 1: Image Courtesy Science Direct

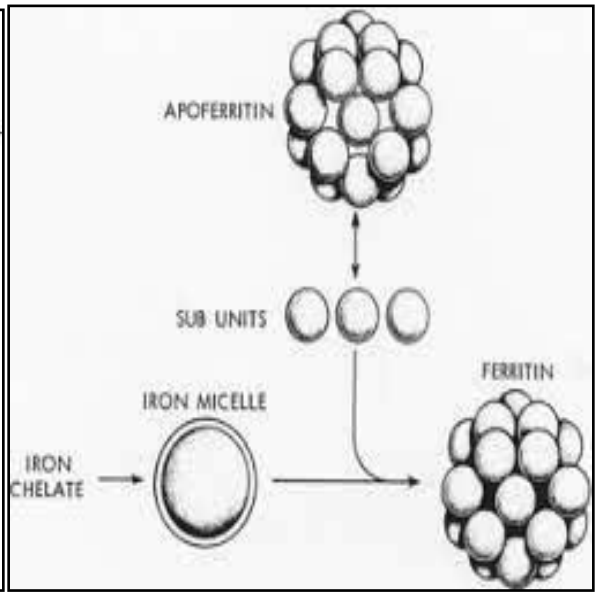

Figure 2: Image Courtesy New England J Medicine

Ferritin as Inflammatory Bio-Marker: General Consideration

Lymphopenia, haemophagocytic lymphohistiocytosis (sHLH) and cytokine storm syndrome are three inflammatory diseases (such as SARS-Covid 19) outcome or co-morbid in which ferritin levels elevated and can detect severity and prediction of poor outcome [14, 15]. It was reported that, based on elevated ferritin levels, body temperature, interleukins etc, a predictive H-score can identify possible development of secondary haemophagocytic lymphohistiocytosis [15]. A recent study carried out in 100 patients, suffering from Covid 19 pneumonia, and categorized into mild, severe and critically ill, showed variable levels of Ferroprotein, with significantly high in critically ill and minutely elevated in mild group of patients [16]. They concluded that not only ferroprotein, but pro-calcitonin, Interleukin also showed correlated elevation and thus suggested to be predictive biomarkers for the severity of the disease. In several dozen studies in late 2019 and 2020, it was reported, discussed and concluded that pathophysiology, evolution of disease pattern, prognosis, treatments and immunological status of SARS Covid 19 with trajectory are still not completely understood and unclear [5,14,15,17]. In a more recent study [18] on thrombosis and bleeding disorders, that are associated with severe Covid 19 infections and are found to be correlated

with altered levels of coagulation factors, however, after disease progression, inflammatory markers, such as Ferritin, Procalcitonin, C-reactive proteins are more relevant indicators of disease progression. Regarding immunity, it is known that T-lymphocytes, such as CD 4+ and CD8+ cytotoxic T cells, are the most significant immune cells to defend against viral infections [19]. Studies carried out in recent year 2020 and 2019, after the outbreak of corona virus pandemic, showed that CD4+ and CD8+ cells are hyper-functioning in more severe cases of SARS Covid 19 infections and might provide disease progression and pathogenesis information [19]. Furthermore, hematological and other lab inflammatory markers, such as procalcitonin (PCT), C-reactive protein (CRP), D-dimer (DD) and Ferritin (Fer) are also noted to be highly elevated in more severe cases of Covid 19 infections.

Ferritin estimation and significance in SARS Covid 19 infections

Whether its pneumonia, haemophagocytic lymphohistiocytosis, Lymphopenia, cytokine storm or simple bleeding disorders after progression of SARS Covid 19 infections, several significant studies reported importance of Ferritin as one of the bio-markers that's been elevated considerably whenever there is disease severity and/or progression [5, 14, 15, 17-19]. It was well reported that patients admitted to Intensive care units (ICUs) after developing Covid 19 complications exhibit more severe alterations of pro-inflammatory markers such as PCT, DD, CRP, IL and Fer [14, 19-22]. Moreover, patients with severe forms of Covid 19 complications also showed liver dysfunction manifested by altered liver enzymes Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin in addition to variations in storage and synthetic activities such as Ferritin overload and coagulation/bleeding disorders [15, 23, 24]. It was also observed that there is a strong correlation between poor prognoses (i.e. non-survivors) and abnormalities in values of pro-inflammatory parameters [14, 15, 19-21, 24].

Hemostatic and thrombotic complications were also reported in most of the serious; ICUs admitted and with poor prognosis patients including bleeding, disseminated intravascular coagulation, thrombocytopenia, non-vessel thrombotic events, arterial thrombosis and venous thromboembolism [18, 25-27]. Elevated or altered levels of biomarkers such as PCT, DD, IL 6, Troponin I, Ferritin and coagulation parameters are indicators of worsening clinical conditions and poor prognosis, specially in case of critically ill, ICU admitted Covid 19 patients suffering from bleeding and thrombotic outcomes [18, 25-27]. It was reported via multivariate analyses that grossly elevated levels of Ferritin, DD, PCT, IL, CRP, ESR and prothrombin time (PT) were predictive of fatality during disease progression in ICU admitted Covid-19 individuals [18, 25-28].

Hyperactivity of immune system, a marked manifestation of SARS-CoV-2 (severe Acute Respiratory Syndrome Coronavirus-2 Covid 19), is also regard as a co-morbid or indicator of poor prognosis, causing rigorous dysregulation of major physiological mechanisms, characterized by altered inflammatory bio-markers such as LDH, Ferritin, DD, PCT, IL, CRP, CD series etc [14, 19, 25-28]. Regarding ferritin, markedly elevated levels were recently been reported to be associated strongly with disease severity, means signification higher in critically ill than non critical patients [17]. Pathogenesis of SARS CoV-2 disease progression involves hyperactive uncontrolled inflammation inducing massive Cytokine release and circulation, conditions very similar to macrophage activation syndrome (MAS) and secondary haemophagocytic lymphohistiocytosis [14, 17, 19, 26-28]. MAS is known to be a very destructive and fetal, mostly after severe viral infections, causing excessive immune hyperactivity, cytokine releasing storm and marked hyperferritinemia [15, 29, 30].

It's been well documented that diabetes not only induces untoward complications in normal bodily functions but also complicates disease severity and progression. In cases of debilitated infectious diseases, diabetes known to stimulate rigorousness of the illness, morbidity and increases chance of mortality [31-33]. Obesity, which is one of the marked sign of Type 2 Diabetes (T2DM) and its consequential outcome, obesity-associated inflammation are basically occurred due to long term exposure to immune imbalance, metabolic dysfunctions, resulting in increased profusion and instigation of innate and adaptive immunity [31-33]. As a consequence of profound instigation of immunity, increased release of inflammatory factors and chemokines/cytokines takes place, causing undue reactions and morbidities. An early study on SARS noted that those patients who were not treated with glucocorticoids showed higher blood glucose levels, suggesting weaker Islets activities and progressing organ dysfunction [31-33]. Furthermore, cytokine storms that known to cause inflammatory response preceding the severity of SARS Covid 19,

induces elevation of inflammatory biomarkers such as IL6, Ferritin, CRP, ESR [30, 34]. Elevated Ferritin levels indicate instigation of monocyte-macrophage system which is an outcome of inflammatory storm [30]. Conclusively, organ dysfunction, coagulation and bleeding disorders, acidosis, and sensitivity for infections (mean low immunity) are consequential events of T2DM and acts as amplification loop for severity of pneumonia from SARS Covid 19 and ultimately poor prognosis.

Conclusion

Present review described diagnostic and prognostic significance of Ferritin, a major iron storing protein, for SARS Covid 19 infection, in addition to its discovery and regulation. It was appraised through specific literature search that, along with other inflammatory markers such as PCT, CRP, D-Dimer, IL6, CD series, ferritin testing is of clinical connotation providing much needed information of disease progression, level of inflammatory response and prognosis. Pneumonia, haemophagocytic lymphohistiocytosis, Lymphopenia, cytokine storm, secondary haemophagocytic lymphohistiocytosis and macrophage activation syndrome are some of the consequential clinical path of Covid 19 infections and thus require Ferritin testing, along with other biomarkers, to asses patients status and treatments courses.

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