Iron deficiency in rheumatoid arthritic patients especially with in the middle age

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Abstract- The present review discuses the iron deficiency in rheumatoid arthritic patients specially with in the middle age grouped (35-55 yrs). Causes of anaemia other than ACD (Anaemia of Chronic Disease) frequently present in Rheumatoid Arthritis, Serum iron, total iron binding capacity and transferrin saturation which are indicators of the iron status. Serum iron, total iron binding capacity and transferrin saturation and serum ferritin are indicator for diagnosis of iron deficiency and response to iron therapy in these patients, Decrease iron absorption was shown to be the result of active Rheumatoid Arthritis rather than serum ferritin, a cause of anaemia of chronic disease (ACD) or iron deficiency. Iron deficiency is detected in rheumatoid arthritic patients. In summary recovery from anaemia occured more frequently in iron depleted anaemic patients than in those with anaemia of chronic disease, seems to have a more serious course of their Rheumatoid Arthritis compared with the healthy controls.
Key words– ACD, IDA, Serum iron, TIBC, Transferrin Saturation, Serum ferritin, middle age

Introduction

Rheumatoid arthritis is a highly inflammatory polyarthritis often leading to joint destruction, deformity and loss of function, Additive; symmetric swelling of peripheral joints is the hallmark of the disease. Extraarticuler features and systemic symptoms can commonly occur and may antedate the onset of joint symptoms. Chronic pain, disability and excess mortality are unfortunate sequelae. The prevalence of Rheumatoid arthritis has been estimated to be approximately 0.8% in the general adult population. The onset of symptoms usually occurs between the ages 30 and 50, with women affected three times more frequently then men. The American college of Rheumatology Subcommittee on Rheumatoid Arthritis estimates that Rheumatoid Arthritis is responsible for 250000 hospitalizations and 9 million physician visits each year in United States [1]. It has also been estimated that 20 to 30% of patients with Rheumatoid Arthritis will become permanently work disabled within three years of diagnosis if left untreated [2]. Rheumatoid Arthritis is, therefore, a source of significant morbidity and decreased quality of life.

Iron Deficiency

Iron is extremely vital to the human beings because of its indispensable role in oxygen transport, DNA synthesis and electron transport [3]. Consequently vital body functions are conditional on appropriate iron stores. Haemoglobin synthesis is particularly iron-dependent [4]. The human body contains approximately 3 to 4gm of iron, with haemoglobin accounting for 60% of the body's total iron. Adult individuals require a relatively constant amount of total body iron. Indeed under usual conditions, very little iron enters or leaves the organism. Iron loss is normally limited to less than 4 mg daily [5] reaching, an average, only 1 mg daily in men and 2 mg in women during the child bearing years. In humans, 80% of the iron demand is related to the daily production of 200 billion new erythrocytes, which requires approximately 20 to 24 mg of iron for the synthesis of hemoglobin. Most of this iron is provided by macrophages through the catabolism of hemoglobin of senescent red blood cells; iron released from aged erythrocytes is recovered from the plasma and delivered to the erythroid marrow [6]. Thus, approximately 90% of iron is the circulation recirculates and there is little iron exchange with other tissues. Iron deficiency is the most common cause of anaemia worldwide. It is estimated that iron-deficiency anaemia (IDA) affects some two billion people causing almost one million deaths each year [7]. Iron deficiency results in the decreased synthesis of important molecules including iron containing enzymes thereby inducing cellular organic functional disturbances. If not corrected in a timely manner, iron deficiency anemia (IDA) will ensue. The consequences of iron deficiency anemia (IDA) range from impaired psychological and physical well-being and decreased occupational abilities to developmental troubles in children and increased morbidity and mortality in some patient populations. Moreover, iron deficiency is a risk factor in various medical settings because it impedes erythropoietic response to acute and chronic anemia.

Mechanisms of Iron Deficiency

Body iron homeostasis is assured by the strict balance between iron input and exertions. The only source for replacing eliminated iron is exogenous iron, an average of 1 of 2 mg are absorbed and eliminated daily under normal

conditions. Iron deficiency occurs if the equilibrium between iron needs and input is not reached because of increased demands, insufficient intake, malabsorption or increased losses, mostly inherent to blood. Iron deficiency can be either absolute or functional. In absolute iron deficiency, the iron stores are depleted, in functional iron deficiency, iron stores, although replete, cannot be mobilized from the macrophages of the reticuloendothelial system (RES). Functional iron deficiency occurs in inflammatory diseases because iron is trapped in the RES as a result of increased secretion of hepcidin, a hormone that controls iron release of erythropoietin (EPD), which places a significant demand on iron stores that may surpass the iron-release capacity of the RES. In our study for review, 105 patients with Rheumatoid Arthritis in which we identified 85% as anaemic. Again among anaemic 60% were found to have Iron Deficiency Anaemia (IDA) and rest 40% to have Anaemia of Chronic Disease (ACD). The differential diagnosis may be difficult, as serum iron levels were low in both types of anaemia. However, Serum Ferritin Test usually distinguishes between IDA and ACD. Anaemia is the most common extraarticular manifestation of Rheumatoid Arthritis, estimated to occur in 30% to 60% of patients [8-10]. Patients with Rheumatoid Arthritis, who are anaemic have evidence of more severe disease, with more involved joints and higher levels of functional disability and pain [11, 12]. Although any type of anemia may be seen in patients with Rheumatoid Arthritis, the two primary type of anemia in Rheumatoid Arthritis appear i.e., Iron Deficiency Anemia and Anemia of Chronic Disease. In their retrospective review of 225 patients with RA, Peters and colleagues inditified 64% as anaemia, in which 77% were found to have ACD and rest 23% to have Iron Deficiency Anemia (IDA). According to our observations, Hb%, serum iron as well as Total Iron Binding Capacity(TIBC) levels are low in the Rheumatoid Arthritic patients as compared to the healthy controls. However, transferrin saturation levels are normal with iron. ACD is characterised, by decreased serum iron, decreased total iron binding capacity which occur in a wide variety of diseases including inflammatory disorders like Rheumatoid Arthritis, whereas serum transferrin saturation happens to be normal with iron. The traditional view is that inflammation is the major mechanism behind the joints destruction. Therefore, the main attention has been directed towards various inflammatory mediators. In clinical practices several indices of inflammatory activity such as Haemoglobin percentage, Erythrocyte Sedimentation Rate (ESR), Differential Leukocyte Count (DLC), Sugar, Urea, Creatinine, Lipid profile, Iron and Total Iron Binding Capacity (TIBC) have been considered as valuable. It has been suggested that joint damage may result from a series of pathological changes unrelated to inflammation. Rheumatoid Arthritis not only, affects peripheral synovial joint mainly but also it is a systemic disease being accompanied by anaemia, an increase, an increase is Erythrocyte Sedimentation Rate (ESR) and weight loss, Vascular, cardiac and pulmonary lesions are also produced. All Rheumatoid Arthritic patients with persistent inflammation develop the anaemia of chronic disease (ACD). This is a mild anaemia associated with chronic inflammatory conditions which is characterised by a disturbance in iron metabolism which results in hypoferrimia despite iron stores that range from adequate to raised. Our findings are supported by the Bentley et al [13] and Hansen et al [14]. We further explain the development of anaemia of chronic disease (ACD) in patients with Rheumatoid Arthritis whose appearance may be related to inflammatory cytokines which cause joint inflammation and interfere with normal red blood cell formation and destruction. Patients with Rheumatoid Arthritis make erythropoietin in response to the inflammatory anaemia, as expected. However, the response is blunted in these patients, with both inadequate production of erythropoietin and inadequate bone marrow responses compared to the people with similar levels of anaemia and no inflammated patients [15-19]. Animal studies suggested that increased levels of the inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor - □ (TNF- □) inhibit erythropoietin production and interfere with erythroid colony forming units in the bone marrow [20-22].

Serum Ferritin

Serum ferritin has been used as the most reliable indicator of iron deficiency in the general population [23]. Ferritin has not been effective as a single diagnostic tool for body iron status in these patients. Single indicators or combinations of them such as ferritin. Serum iron, TIBC and MCV were suggested as markers of iron deficiency. As observed from our study serum ferritin i.e. iron storage protein ferritin may be glycosylated within hepatocytes and secreted behaving as an acute phase protein in inflammation [24]. As well as increase in the synthesis of ferritin, interleukin-1 contributes towards the hypoferrimia by increasing lactoferrin production from the specific granules of neutrophils.(25) During inflammation lactoferrin competes with transferrin for iron (Particularly of the low pH existing in inflammatory sites [26] and it does not transfer iron to erythropoietic cells [27] only to macrophages [28] was decreased by 76.43% as compared the control subjects. This study suggested that, in chronic inflammatory diseases, Iron retention is increased by the mononuclear phagocyte system and iron

utilization is impaired secondary to decreased iron uptake by erythroblasts. This result might suggest more severe disease in the former. Muirden was the first to suggest that the large amounts of iron sequestered in the rheumatoid synovial membrane may contribute towards the anaemia of the disease. The author found large amounts of iron loaded ferritin molecules, particularly in type A synovial lining cells. The ferritin was scattered throughout the cell cytoplasm but was often concentrated in lysosomes. All the synovial biopsy specimens which contained iron were removed from patients who were either severely or moderately anaemic [29]. Ball et al detected a mild inflammatory reaction in the synovial membrane with some synovial membrane with some synovial proliferation five to eighteen hours after the iron dextran injection. The iron was in the form of ferritin and haemosiderin and persisted for these months after the injection [30]. Muirden and coworkers showed that synovial cells in culture can ingest haemoglobin prepared from heamolysed red cells and the subsequent appearance of ferritin in these cells implied that they were able to synthesise apoferritin. The authors suggested that both the synthesis of ferritin and breakdown of Haemoglobin take place within the same lysosome and that iron from lysed erythrocytes is likely to be an important source of the iron deposits in the rheumatoid synovid [31]. Muirden and Senator suggested that iron deposits in Rheumatoid Arthritis arise from continued oozing of blood from the vascular granulation tissue into the synovial cavity [32]. In highly inflamed rheumatoid joints, simple bearing or the stress of motion may be the hyperplastic villi and synovial fold to bleeding. These large deposits only have a considerable contributory to anaemia and pathogenesis of this disease.

Summary

Iron, which is present in the rheumatoid Synovial membrane mainly in the form of ferritin. Ferritin is also found in the synovial fluid, where its concentration correlates with levels of other indices intra-actical disease activity such as synovial immune complex. Iron concentration within synovial membrane does not correlate closely the duration of the disease. This may be become such iron originates, at least in part, microbleeding. Iron concentrations do correlate however, with erosive bone damage. In Rheumatoid Arthritis disease the presence of ferritin haemosiderin iron in the synovial membrane implies a poor prognosis.

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Table 1-A comparative analysis of RA factor, Haemoglobin%, Serum iron, TIBC and ferritin in Rheumatoid Arthritic patients (Mean ±SD)

S.N.	Variables	Control Group (35-55yrs) n=80	Study Group (35-55yrs.) n=80
		(55 females, 25 males)	(55 females, 25 males)
1	Hb (gm%)	13.25 ± 0.901	8.72 ± 0.509
2	Serum Iron (mg/dl)	129.89 ± 22.87	31.33 ± 5.42
3	Serum TIBC (mg/dl)	340.66 ± 33.516	112.8 ± 25.33
4	Serum Ferritin (ng/ml)	123.76 ± 16.15	29.17 ± 15.33

P <0.001 Highly Significant, *P>0.001 Significant