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Clinical evaluation of serum iron levels in rheumatoid arthritis patients in darbhanga medical college and hospital

Dr. Devendra Kumar Sinha
Assistant Professor, Department of General Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

Abstract
Ferritin a key protein of iron metabolism is capable of dual function in iron detoxification and iron storage present in serum and biological fluids. It is a multimeric protein consists of 24 subunits of types H and L which surrounds a cavity in which iron can be stored in a readily available non-toxic form. The synthesis of ferritin is regulated by cytokines at various levels of protein synthesis, during cellular differentiation, proliferation and inflammation. The expression of ferritin is also regulated by hormones, growth factors, second messengers and hypoxia. Both oxidant and antioxidants response inducers regulate ferritin gene transcription. During certain conditions the deregulation of ferritin cause this intracellular iron storage protein to act as prooxidant. Therefore the present study aims to determine the ferritin level in RA and its response to oxidative stress.
The present study was planned in Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar from July 2018 to Feb 2019. Total 40 patients were enrolled in the present study. The patients were divided in two groups for comparative study of different parameters. The Group I consist of 20 patients diagnosed with Rheumatoid arthritis were enrolled for the study. The group B consist of 20 control patients for comparative evaluation.
The present study concludes that anemia is a common extra articular manifestation of Rheumatoid arthritis and anemia of chronic disease is the commonest type of anemia in Rheumatoid arthritis, however there is a high prevalence of iron deficiency anemia in RA in this part of country. There is no known prevention for iron deficiency anaemia in rheumatoid arthritis (RA) patients other than the reduction of contributory factors. Therapy goals are to reduce pain and inflammation and improve quality of life. Surgery to repair, replace or fuse joints may help in serious conditions.

Keywords: Rheumatoid Arthritis, Iron Deficiency, Haemoglobin, Iron, etc

Introduction
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. An external trigger (eg, cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals. See the image below.
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. The hallmark feature of this condition is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, though any joint lined by a synovial membrane may be involved. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant.
No laboratory test results are pathognomonic for RA, but the presence of anti-cyclic citrullinated protein antibody (ACPA) and rheumatoid factor (RF) is highly specific for this condition.
Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present [1]. Often, symptoms come on gradually over weeks to months [2].
While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage [1]. The diagnosis is made mostly on the basis of a person's signs and symptoms [2]. X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms [1]. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others [3-4].
The goals of treatment are to reduce pain, decrease inflammation, and improve a person's overall functioning [5]. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. Disease-modifying ant rheumatic drugs (DMARDs), such as hydroxychloroquine and methotrexate, may be used to try to slow the progression of disease [1]. Biological DMARDs may be used when disease does not respond to other treatments [6]. However, they may have a greater rate of adverse effects [7]. Surgery to repair, replace, or fuse joints may help in certain situations [1]. Most alternative medicine treatments are not supported by evidence [8, 9].

Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender and warm, and stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are the small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function [2].

RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, such as osteoarthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent.[citation needed] The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic [10]. The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical [11].

As the pathology progresses the inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in osteoarthritis, include ulnar deviation, boutonniere deformity (also "buttonhole deformity", flexion of proximal interphalangeal joint and extension of distal interphalangeal joint of the hand), swan neck deformity (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal joint) and "Z-thumb." "Z-thumb" or "Z-deformity" consists of hyperextension of the interphalangeal joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives a "Z" appearance to the thumb [16]. 1098 The hammer toe deformity may be seen. In the worst case, joints are known as arthritis mutilans due to the mutilating nature of the deformities [12]. He disease progresses by forming granulation tissue at the edges of the synovial lining, pannus with extensive angiogenesis and enzymes causing tissue damage [45]. The synovium thickens, cartilage and underlying bone disintegrate, and the joint deteriorates, with raised calprotectin levels serving as a biomarker of these events. Cytokines and chemokines attract and accumulate immune cells, i.e. activated T- and B cells, monocytes and macrophages from activated fibroblasts, in the joint space. By signalling through RANKL and RANK, they eventually trigger osteoclast production, which degrades bone tissue [13].

Tumor necrosis factor alpha (TNF-α) plays a major role and several theories exist on how TNF release happens in RA. TNF-α is a proinflammatory cytokine that plays a pivotal role in regulating the inflammatory response in rheumatoid arthritis (RA).If TNF release is stimulated by B cell products in the form of RF or ACPA -containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity. As of 1999, if TNF release is stimulated by T cell products such as interleukin-17 it might be closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful. Although TNF appears to be the dominant chemical mediator other cytokines are involved in inflammation in RA, because blocking TNF does not benefit all persons and all tissues, particularly lung disease and nodules may get worse. Blocking IL-1, IL-15 and IL-6 have beneficial effects and IL-17 may be important [14].

Serum iron is a medical laboratory test that measures the amount of circulating iron that is bound to transferrin (90%) and serum ferritin (10%). Clinicians order this laboratory test when they are concerned about iron deficiency, which can cause anemia and other problems. 65% of the iron in the body is bound up in hemoglobin molecules in red blood cells. About 4% is bound up in myoglobin molecules. Around 30% of the iron in the body is stored as ferritin or hemosiderin in the spleen, the bone marrow and the liver. Small amounts of iron can be found in other molecules in cells throughout the body. None of this iron is directly accessible by testing the serum. However, some iron is circulating in the serum. Transferrin is a molecule produced by the liver that binds one or two iron (III) ions, i.e. ferric iron, Fe3+; transferrin is essential if stored iron is to be moved and used.

Most of the time, about 30% of the available sites on the transferrin molecule are filled. The test for serum iron uses blood drawn from veins to measure the iron molecules that are bound to transferrin, and circulating in the blood. The extent to which sites on transferrin molecules are filled by iron ions can be another helpful clinical indicator, known as percent transferrin saturation. Another lab test saturates the sample to measure the total amount of transferrin; this test is called total iron-binding capacity (TIBC). These three tests are generally done at the same time, and taken together are an important part of the diagnostic process for conditions such as anemia, iron deficiency anemia, anemia of chronic disease and Haemochromatosis.

Ferritin a key protein of iron metabolism is capable of dual function in iron detoxification and iron storage present in serum and biological fluids. It is a multimeric protein consists of 24 subunits of types H and L which surrounds a cavity in which iron can be stored in a readily available non-toxic form. The synthesis of ferritin is regulated by cytokines at various levels of protein synthesis, during cellular differentiation, proliferation and inflammation. The expression of ferritin is also regulated by hormones, growth factors, second messengers and hypoxia. Both oxidant and antioxidants response inducers regulate ferritin gene transcription. During certain conditions the deregulation of ferritin cause this intracellular iron storage protein to act as prooxidant. Therefore the present study aims to determine the ferritin level in RA and its response to oxidative stress.

Methodology

The present study was planned in Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar from July 2018 to Feb 2019 Total 40 patients were enrolled in the present study. The patients were divided in two groups for comparative study of different parameters. The Group I consist of 20 patients diagnosed with Rheumatoid arthritis were enrolled for the study. The group B consist of 20 control patients for comparative evaluation.

Six milliliters of intravenous blood were gathered from

every subjects and whole blood count (CBC) was assessed utilizing mechanized haematology analyzer (Mythic™). Serum samples were obtained after centrifugation (3000 rpm for ten minutes) and after that kept with deep freeze in Eppendorf tube until investigation.
All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.
Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Patients who satisfied the American Rheumatologic association criteria 1987, irrespective of haematological signs present or not. Age group 30 to 55 years irrespective of sex. Duration of disease up to 2 years.

Exclusion criteria: The patients with any of the following diseases were excluded:
Haematological malignancies; Haemolytic anemia; Renal insufficiency; Liver disease; Endocrine disorders e.g., hypothyroidism, hyperthyroidism, pituitary failure, Vitamin B12 or folate deficiency, History of acute blood loss, blood transfusion, receiving iron supplementation within 1 month.

Results & Discussion
Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and, in some cases, extra articular involvement [15]. Extra-articular manifestations can be detected in almost any organ system, causing considerable disease related morbidity and interference with quality of life. Anemia is a frequently occurring extra-articular manifestation of RA, being mostly of the normochromic and normocytic type. Anemia is multifactorial, reflected in dimorphic appearance and wide red cell distribution width. Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are the most important types of anemia in RA patients.
Serum ferritin has been used as the most reliable indicator of iron deficiency in the general population [26]. 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 [17]. 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 [18]. During inflammation lactoferrin competes with transferrin for iron (Particularly of the low pH existing in inflammatory sites [19] and it does not transfer iron to erythropoietic cells [20] only to macrophages [21] 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.

Table 1: Demographic Details

Groups	Group I	Group II
Variables	**Study Group**	**Control Group**
No. of Patients	20	20
Age		
30 – 40 years	3	2
40 – 55 years	7	6
55 years above	10	12
Males	10	12
Females	10	8

Table 2: Serum Findings

Groups	Group I	Group II
Variables	**Study Group**	**Control Group**
No. of Patients	20	20
Hb (gm %)	8.9 – 9.3	10.9 – 14.6
Serum Iron (mg/dl)	27.5- 43.5	101.5 – 157.8
Serum TIBC (mg/dl)	79.6 – 151.6	291.8 – 343.5
Serum Ferritin (ng/ml)	17.8 – 38.9	108.9 – 138.5

It is difficult to evaluate anemia in patients with inflammation as conventional laboratory tests for iron status are often unable to differentiate ACD (anemia of chronic disease) from IDA. S. ferritin is the most commonly used single laboratory test to diagnose iron deficiency as its concentration is roughly proportional to the iron stores, but there is no agreement on the best lower reference value for absent iron stores in the presence of ACD as its level increases in response to underlying inflammation. As a consequence, a wide range of reference limits for S. ferritin have been suggested to diagnose iron deficiency in patients with chronic inflammation [22-23]. The gold standard for assessing iron status is staining the bone marrow iron with Perl's stain. However, this procedure is invasive, expensive and painful.
S ferritin is the most specific marker of iron stores, but there occurs a relatively little change in its level after stores are fully depleted whereas sTfR levels rise with increase in iron deficiency. This indicates that S. ferritin is the most sensitive index of iron status whereas sTfR is more sensitive when there is functional iron deficiency. Moreover, sTfR levels also reflect the rate of erythropoiesis, so its specificity decreases as a sole marker of iron deficiency. Thus because of this reciprocal relationship between sTfR and S.ferritin, the Serum TfR / ferritin ratio reflects the iron status over the entire range. STfR levels are expected to be highest in IDA as reported earlier by Dimitriou H *et al*. [24], by Malope B *et al*. [25] in their study of 561 preschool children and also by Angeles *et al*. [26] and Hanif E *et al*. [27] in different studies.
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 [28]. 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 [29]. 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 [30].

Patel *et al*., (2011) interphalangeal was concomitant with this study when they describe the coexistence of iron insufficiency with the severe ferritin elevation as distinguishing of SLE. The combined effect has clinical significance and permits assumptions around the occurrence of hyperferritinaemia despite obvious iron depletion. The co-occurrence of iron insufficiency must be deliberated at what time estimating the patient with anaemia of chronic diseases despite the ferritin concentrations are increased numerous hundredfold. Additional perceptions on the metabolism of ferritin are proposed by the probability that the severe hyperferritinaemia in inflammatory status of SLE disease was approximately whol of the iron-free apoferritin form [31].

Data from Masson provide a reasonable linkage amongst interleukin-6 generation and the progression of anaemia in patients with the long-lasting disease. This cytokine inhibits the quantity of reticulocytes by interfering with the erythropoiesis inside haemopoiteic tissues and depresses the iron amounts, and those combined effect defects could be ameliorated by administration of interleukin-6 blockers [32]. Dakhil and Mezher (2014) reported that inflammatory hypoferraemia is facilitated by interleukin-6 which stimulates production of hepcidin, a hormone which regulate the iron metabolism [33].

Conclusion

The present study concludes that anemia is a common extra articular manifestation of Rheumatoid arthritis and anemia of chronic disease is the commonest type of anemia in Rheumatoid arthritis, however there is a high prevalence of iron deficiency anemia in RA in this part of country. There is no known prevention for iron deficiency anaemia in rheumatoid arthritis (RA) patients other than the reduction of contributory factors. Therapy goals are to reduce pain and inflammation and improve quality of life. Surgery to repair, replace or fuse joints may help in serious conditions.

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