Madonna University Journal of Medicine and Health Sciences. Volume 2 issue 2(2022), Pp. 41-74© Madonna University Press, Inc.
2022http://madonnauniversity.edu.ng/journals/index.php/medicine

AN UPADTE ON INTERLEUKIN 6 AND IRON STATUS OF VOLLEYBALL PLAYERS

*Obeagu Emmanuel Ifeanyi[1], Obeagu Getrude Uzoma[2], Emeonye Odochi Peace[3] and Jakheng Shango Patience Emmanuel[4,5]

[1]Department of Medical Laboratory Science, Imo State University, Owerri, Imo State, Nigeria.

[2]Department of Nursing Science, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria.

[3]Department of Nursing Science, Abia State University, Uturu, Abia State, Nigeria.

[4]Department of Microbiology, Kampala International University, Uganda

[5]Institute of Leather and Science and Technology, Zaria, Kaduna State, Nigeria

emmanuelobeagu@yahoo.com

Abstract

Cytokines are released at the site of inflammation and facilitate an influx of lymphocytes, neutrophils, monocytes, and other cells that participate in the clearance of the antigen and healing. The local inflammatory response is accompanied by a

Obeagu, E.I., Obeagu, G.U., Emeonye, O.P. and Jakheng,S.P.E.(2022).An update on interleukin 6 and iron status of volleyball players.Madonna University Journal of Medicine and Health Sciences. 2(2): 41-74

systemic response known as the acute phase response. Interleukin-6 is produced in larger amounts than any other cytokine in relation to exercise. IL-6 in response to long duration exercise is independent of muscle damage, whereas muscle damage as such is followed by repair mechanisms including invasion of macrophages into the muscle leading to IL-6 production. Interleukin 6 has a great association with iron through the regulatory mechanisms of hepcidin. The review used different research search engines such Google scholar, PubMed, Scopus, Clarivate analytics, etc. It was revealed the interleukin 6 and iron levels were raised in the volleyball players after playing due to inflammation of the muscles. Interleukin 6 and iron should be monitored in those playing volleyball.

Keywords*: interleukin 6, iron, volleyball, inflammation, healing, antigens, cytokines*

Introduction

Cytokines are released at the site of inflammation and facilitate an influx of lymphocytes, neutrophils, monocytes, and other cells that participate in the clearance of the antigen and healing. The local inflammatory response is accompanied by a systemic response known as the acute phase response. This response includes the production of a large number of hepatocyte-derived acute phase proteins, e.g. C-reactive protein (CRP). Injection of tumour necrosis factor (TNF)-alpha or interleukin (IL)-1beta into laboratory animals or humans will produce most if not all aspects of the acute phase response (Dinarello, 1992). These cytokines are, therefore, usually referred to as "inflammatory" or "proinflammatory cytokines." IL-6 has been classified as both a pro- and an anti-inflammatory cytokine, but the most recent view is that IL-6 has primarily anti-inflammatory effects (Barton, 1997; Xing et *al.*, 1998). Infusion of IL-6 into humans will result in fever but does not cause shock or

capillary-leakage-like syndrome as observed with the prototypical pro-inflammatory cytokines, IL-1 and TNF-alpha (Mastorakos et *al.*, 1993). Unlike IL-1 and TNF-alpha, IL-6 do not upregulate major inflammatory mediators such as nitric oxide or matrix metalloproteinases (Barton, 1997). Rather, IL-6 appears to be the primary inducer of the hepatocyte derived acute-phase proteins, many of which have anti-inflammatory properties (Barton, 1997). IL-6 directly inhibits the expression of TNF alpha and IL-1 and, furthermore, IL-6 is a potent inducer of the interleukin-1 receptor antagonist (IL-1ra), which exerts anti-inflammatory activity by blocking IL-1receptors and thereby prevents signal-transduction of the pro-inflammatory IL-1 (Barton, 1997).

The Cytokine Response to Exercise

Recent studies show that several cytokines can be detected in plasma during and after strenuous exercise (Ostrowski *et al.*, 1998; Ostrowski *et al.*, 1999; Ostrowski *et al.*, 1998). After a marathon race, TNF-alpha and IL-1beta levels increase two-fold and the IL-6 level increases up to 100-fold; this is followed by a marked increase in the concentration of IL-1ra (Ostrowski *et al.*, 1999; Ostrowski *et al.*, 1998). Thus, the increase in TNF-alpha and IL-1beta levels is accompanied by a dramatic increase in IL-6. This release is balanced by the release of cytokine inhibitors (IL-1ra and TNF-receptors) as well as the anti-inflammatory cytokine IL-10.

Characteristics of the IL-6 Response to Exercise

Interleukin-6 is produced in larger amounts than any other cytokine in relation to exercise. Northoff and Berg (1991) were the first to suggest that IL-6 might be involved in sports.

The IL-6 Response to Exercise and Muscle Damage

Previously, we found that peak IL-6 was associated with muscle damage using an eccentric exercise model in which the plasma creatine kinase (CK) activity peaked at day 4 after the exercise (Bruunsgaard *et al.*, 1997). These data are in agreement with results showing that in eccentric exercise, a statistical association exists between IL-6 levels 2 hours after eccentric exercise and delayed onset muscle soreness the day after (MacIntyre *et al.*, 2001). However, later studies from our group using exercise models in which CK peaked one day after exercise failed to show an association between peak-IL-6 and peak CK levels (Ostrowski *et al.*, 1998; Ostrowski *et al.*, 1999). It is most likely that the huge and immediate increase in IL-6 in response to long duration exercise is independent of muscle damage, whereas muscle damage as such is followed by repair mechanisms including invasion of macrophages into the muscle leading to IL-6 production.

Intensity of Exercise—Role of Adrenaline

Data from the Copenhagen Marathon Race (1996, 1997 and 1998; $n = 56$) suggests that there is a negative correlation between running time and the increase in plasma IL-6 (Pedersen et *al.*, 1998). Thus, runners with the fastest running times showed the highest IL-6 response. An animal study suggested that the increase in adrenaline during stress was responsible for the increase in IL-6 (DeRijk *et al.*, 1994).

Muscle-Derived IL-6

A study was performed to test the hypothesis that cytokines are produced in skeletal muscle in response to intense long-duration exercise (Ostrowski et *al.*, 1998). Muscle biopsies and blood samples were collected before and after a marathon race. The levels of IL-6 and IL-1ra proteins were markedly increased after the exercise. The levels of IL-6 decreased, whereas IL-1ra increased further 2 hours after the exercise. A comparative polymerase chain reaction (PCR) technique was established to detect mRNA for cytokines in skeletal muscle biopsies and blood mononuclear cells (BMNC). Before exercise, mRNA for IL-6 could not be detected in muscle or BMNC. In contrast, mRNA for IL-6 was detected in muscle biopsies after exercise. The finding of IL-6 mRNA in muscle in response to exercise was confirmed in a rat exercise model, using a quantitative competitive real-time-PCR method (Jonsdottir *et al.*, 2000). In this model, rats were subjected to electrically-induced eccentric or concentric contractions of the one hind leg, while the other leg remained at rest. Both the eccentric and concentric contractions resulted in elevated levels of IL-6 mRNA in the exercised muscle, whereas the level in the resting leg was not elevated. The finding of the same level of IL-6 mRNA in both concentrically and eccentrically exercised muscle indicates that cytokine production cannot be as closely related to muscle damage as first thought. It does, however, appears that the local IL-6 production is connected with exercising muscle and is not due to a systemic effect because IL-6 mRNA was elevated only in the muscle from the exercising leg and not in the other resting leg. Unpublished data from our group further demonstrates that muscle contractions induce transcription of IL-6. However, the finding that small amounts of IL- 6 are released within a few minutes of exercise (Nielsen *et al.*, 1996) suggests that exercise also influences the translation and/or the release of IL-

6. We still need to identify the cell source of IL-6 in working skeletal muscles and to identify the signal transduction pathways from muscle contraction to activation of the IL-6 gene. Interestingly, IL-1beta and IL-6 gene expression is markedly up-regulated during limb ischemia (Testa *et al.*, 2000), and since hypoxia is linked with increased plasma levels of IL-6 (Klausen *et al.*, 2001), it is possible that local hypoxemia plays a mechanistic role in exercise- induced IL-6 production.

Muscle-Derived IL-6—Possible Biological Functions

In severe infections, the main role of IL-6 is to stimulate the liver to produce acute phase proteins, such as C-reactive protein. The exercise-induced elevation in IL-6 results in only a minor effect on the liver production of acute phase proteins (Pedersen and Hoffman- Goetz, 2000). The exercise-induced increase in IL-6 appears to be a tight function of exercise duration. IL-6 has been shown to markedly inhibit insulin-stimulated increases in glycogen deposition in rat hepatocyte cultures (Kanemaki *et al.*, 1998). Furthermore, IL-6 has been shown to inhibit glycogen synthase activity and accelerate glycogen phosphorylase activity (Kanemaki *et al.*, 1998). It has further been demonstrated that injection of recombinant human IL-6 (rhIL-6) into humans increases the fasting blood glucose concentration in a dose-dependent manner (Tsigos et *al.*, 1997). Another study using human subjects showed increased hepatic glucose output in response to injection of rhIL-6, concomitantly with a higher glucose metabolism (Stouthard *et al.*, 1995). It has also been shown that consuming carbohydrate during exercise diminishes the exercise-induced increase in IL-6 (Nehlsen Cannarella *et al.*, 1997). Altogether, these studies suggest that IL-6 may work in a hormonelike fashion and it is likely that IL-6 represents an

important link between contracting skeletal muscles and the regulation of hepatic glucose output. Furthermore, it has been demonstrated that IL-6 stimulates lipolysis in fat cells (Mattcs, 1999) and it is therefore possible that muscle-derived IL-6 also plays a role in lipid metabolism. Future studies should also address the question of how IL-6 interacts with cytokines produced by inflammatory cells and by adipose tissue.

Iron deficiency

Iron deficiency is the most common single nutrient deficiency disease in the world and is a major concern for ≈15% of the world's population (DeMaeyer and Adiels-Tegman, 1985). The commonly used definition for anemia, regardless of its cause, is a low hemoglobin concentration. If iron deficiency is an underlying etiology, then by definition an individual must have depleted iron stores, low ferritin in plasma or decreased stainable iron in bone marrow, and inadequate delivery of iron to tissues as characterized by low transferrin saturation, a high erythrocyte protoporphyrin concentration, and an elevated transferrin receptor concentration (INACG, 1985; Skikne *et al.,* 1990).

Iron deficiency can be defined as occurring when the body's iron stores become depleted and a restricted supply of iron to various tissues becomes apparent (Bothwell *et al.,* 1979). The clear consequences of iron depletion are a reduction in oxygen transport capacity and a reduction in oxidative capacity at the cellular level of functioning. The process by which iron stores are depleted may occur rapidly or very slowly and depends on the balance between iron intake and iron requirements.

From the evidence already published in the scientific literature, it is reasonable to conclude that iron intake is marginal or inadequate in numerous females who engage in regular physical exercise. In many females, iron depletion is undoubtedly related to both quantities of food and the inherent density of iron in the typical American diet, as well as the decision by many persons to remove meat from their diet (Weaver and Rajaram, 1992; Cook, 1994).

DIETARY IRON

Clearly, daily iron intake depends on the composition of food consumed and the quantity of iron therein. Several inhibitors and a small number of enhancers of iron absorption are now known to exist. Iron absorption increases in individuals who have depleted iron status, and this internal regulator of absorption may be more important than any particular constituents of the food supply. Basal obligatory losses in humans are ≈1 mg Fe/d and must be replaced by an equivalent amount of iron derived from the diet (Cook *et al.*, 1991).

The typical Western diet provides an average of 6 mg of haeme and nonhaeme iron per 4120 kJ of energy intake. The bioavailability of iron is both a function of its chemical form and the presence of food items that promote or inhibit its absorption. Ascorbic acid and meat are known as the most powerful of these enhancers of nonhaeme iron absorption, whereas the list of inhibitors is much longer. In contrast to heme iron absorption, many factors affect nonhaeme iron absorption and include bran; hemicellulose; cellulose; pectin; phytic acid, which is found in wheat and soy

products; and polyphenolic compounds (Carpenter and Mahoney, 1992; Davis *et al.*, 1992).

Haeme iron is an important dietary source of iron because it is more effectively absorbed than is nonhaeme iron; thus, vegetarians can be at a relatively greater risk for iron deficiency, especially if food restriction is part of the dietary self-control exerted by female athletes. From 5% to 35% of haeme iron is absorbed from a single meal, whereas nonhaeme iron absorption from a single meal can range from 2% to 20%, depending on the iron status of the individual and the ratio of enhancers and promoters in the diet. Thus, although haeme iron constitutes only ≈10% of the iron found in the diet, haeme iron may provide up to one-third of absorbed dietary iron (Bjorn-Rasmussen et *al.*, 1974; Conrad, 1993). Haeme iron appears to be affected only by animal proteins, which facilitate its absorption, and calcium, which inhibits its absorption (Hallberg et *al.*, 1993).

The absorption of supplemental iron depends on the type of preparation used. The amount of iron that is bioavailable from multimineral preparations, especially when calcium salts are used, is less than that absorbed during the administration of iron alone (Seligman et *al.*, 1983; Hallberg *et al.*, 1992). These preparations may provide less iron than suspected because the bioavailability in practice is less than would be predicted if only an iron preparation was used. Additionally, multivitamin and mineral preparations are often consumed with a meal or with coffee and tea. These additional factors may further reduce the net absorption of iron. One of the frequent complaints voiced by iron supplement users about either over-the-counter iron supplements or the prescribed higher-dose iron supplements are the side effects of

constipation and gastrointestinal upset (Solvell, 1996). Because many young female athletes are told to consume iron supplements in doses of >50 mg Fe/d, noncompliance can be a significant issue. Lower-dose administration of supplements containing ≤125 mg ferrous sulfate (39 mg Fe) per day prevented the decrease in serum ferritin that was attributable to altered iron balance in competitive female swimmers (Brigham *et al.,* 1993). These swimmers, who had no complaints of gastrointestinal distress, were in contrast to the frequent complaints noted when therapeutic doses of iron were used (Solvell, 1996). Reports of iron supplementation on a weekly or biweekly basis in Third World populations showed the strong possibility that less frequent use of iron supplements can still provide positive effects without gastrointestinal distress (Viteri, 1995; Gross *et al.* 1994). No known systemic studies have used this approach with athletes, although the approach holds great promise for improving long-term efficacy and improvement of iron status.

CONSEQUENCES OF POOR IRON STATUS

Many organs show morphologic, physiologic, and biochemical changes with iron deficiency in a manner related to the turnover of essential iron-containing proteins. Sometimes this occurs even before a significant decrease in hemoglobin concentration occurs (Dallman, 1986). Iron deficiency is associated with altered metabolic processes, including mitochondrial electron transport, neurotransmitter synthesis, protein synthesis, organogenesis, and others. The overt physical manifestations of chronic iron deficiency are glossitis, angular stomatitis, koilonychia (spoon nails), blue sclera, esophageal webbing (Plummer-Vinson syndrome), and anemia. Behavioral disturbances such as pica [abnormal

consumption of dirt (geophagia) and ice (pagophagia)] are often present in persons with iron deficiency, although a biologic explanation is lacking.

It is also important to delineate whether exercise itself may alter iron status and whether such alterations are detrimental to athletic performance or to the health of an athlete. Although a multitude of laboratories worldwide have contributed to a broad-based accumulation of knowledge in these areas (Dallman, 1986; Tobin and Beard, 1996), an analysis of >2 decades of research illustrates several central points. First, it is clear that reductions in hemoglobin concentration and tissue iron content can be detrimental to exercise performance. Second, it is documented that iron status is negatively altered in many populations of chronically exercising individuals. Third, women may have an increased prevalence of exercise-related alterations in body iron because of a net negative iron balance.

The role of haeme and nonhaeme iron in biological function and work performance has been elucidated through human and animal experiments, and several classic reviews have been published (Finch and Huebers, 1982; Dallman, 1982) and updated (Azevedo *et al.*,1989). Not surprisingly, hemoglobin iron, when lacking, can profoundly alter physical work performance via a decrease in oxygen transport to exercising muscle. What is intriguing, however, is that although nonhaeme iron associated with enzyme systems constitutes only 1% of total body iron, profound deficits of these cellular enzymes per se may have detrimental effects on athletic performance. Studies illustrate that maximal oxygen uptake ($\dot{V}O_2max$) is determined primarily by the oxygen-carrying capacity of the blood and is thus correlated with the degree of anemia. Endurance performance at reduced exercise intensities,

however, is more closely related to tissue iron concentrations because of the strong association between the ability to maintain prolonged submaximal exercise and the activity of iron-dependent oxidative enzymes.

Several of the well-known consequences of iron deficiency that occur after the depletion of iron stores are a decline in hemoglobin concentration, decreased mean corpuscular hemoglobin concentration, decreased size and volume of new red cells, reduced myoglobin, and reduced amounts of both iron-sulfur and haeme iron-containing cytochromes within cells. Diffusion of dioxygen from hemoglobin into tissue becomes limited as a result of fewer erythrocytes, increased membrane diffusivity, and decreased tissue myoglobin concentration. In severe anemia, oxygen transport is clearly limiting to tissue oxidative function at anything but the resting condition (Dallman, 1986), despite a right-shifted hemoglobin–O_2 dissociation curve and increased cardiac output. Tissue extraction of oxygen is increased by this compensation and partial oxygen pressure in mixed venous blood is significantly lower in anemic individuals. The very significant decrease in myoglobin and other iron-containing proteins in the skeletal muscle of persons with iron deficiency anemia contribute significantly to the decline in muscle aerobic capacity (Dallman, 1982).

Several studies conducted documented altered iron status in athletes but questioned whether such alterations were physiologically detrimental. That is, the investigators questioned whether exercise training itself leads to a negative iron balance with subsequent deleterious effects on exercise performance. Wijn e*t al.* (1971) measured haemoglobin, packed cell volume, serum iron, and iron-binding capacity in selected

athletes and compared these with the hematologic profile of officials during the 1968 Olympic Games. These data illustrated iron deficiency anemia in 2% of male and in 2.5% of female athletes, and mild anemia without signs of iron depletion in 3% of the athletic population. Many other descriptive studies also demonstrated a significant decrease in red blood cell number and a decrease in hemoglobin and ferritin concentrations in athletes (Tobin and Beard, 1996). In many cases, the runners were the most affected group. The authors speculated that a recurring haemoglobinuria might produce diminished iron reserves in middle- and long-distance runners. Radomski et al (Radomski *et al.*, 1980) evaluated hematologic changes in physically fit young soldiers who marched 35 km/d for 6 d at 35% of their $\dot{V}O_2$max.

Subsequent investigations have supported the results of these early studies and have demonstrated a reduction in hemoglobin and haematocrit in certain athletic populations, although clear negative consequences with regard to performance are lacking. Newhouse et al (Newhouse *et al.*, 1989; Newhouse *et al.*, 1993) and Newhouse and Clement (Newhouse and Clement, 1995) elucidated the implications of iron deficiency in female athletes. Others have noted an increased incidence of decreased serum ferritin in female runners (Nielsen and Nachtigall D, 1998; Bourque *et al.*, 1997). In a summary of surveys, serum ferritin concentrations in female athletes were found to be <12 mg/L in 35%, <25 mg/L in 82%, and <30 mg/L in 60%, as compared with their sedentary counterparts from the nonathletic female population. Although estimations of the precise prevalence rates differ, an increased incidence of reduced serum ferritin seems to be a repeatable observation among

laboratories in this population. These results may be influenced by menstrual flow and perhaps dietary iron intake. The issue of menstrual flow is often overlooked in estimates of loss of body iron in female athletes. The most compelling evidence for iron depletion is the observation of altered serum ferritin concentrations, which are generally lower in female athletes.

What these investigations do not demonstrate, however, is a clinically subnormal or reduced serum ferritin concentration concurrent with a demonstrated functional consequence in the absence of overt anemia. That is, the drop in ferritin is not detrimental to the physical performance of the athlete. Studies determined that simple dietary changes can prevent the decrease in ferritin during very modest exercise. The daily consumption of a single meat-containing meal was sufficient to maintain ferritin during a prolonged study when aerobic dance was used as the exercise modality. Moderate doses of over-the-counter doses of ferrous sulfate, 39 mg elemental Fe, or 125 mg $FeSO_4$, are sufficient to prevent the drop in ferritin in highly trained college swimmers. This is in contrast to much higher doses administered by others to prevent training-induced declines in iron status (Lyle *et al.,* 1992).

Several investigators have proposed mechanisms by which iron balance could be affected by intense physical exercise (Siegel *et al.,* 1979; Stewart *et al.,* 1984; Brune et *al.,* 1986). Explanations include increased gastrointestinal blood loss after running and haematuria as a result of erythrocyte rupture within the foot during running. The possibility of increased red cell turnover in athletes is supported by the ferrokinetic measurements conducted by Ehn *et al*. (1980). They demonstrated that the whole-

body loss of radioactive iron occurred ≈20% faster in female athletes than in nonathletes, and both were faster than that in adult men. When the rate of loss of iron from the red cell mass is examined in highly controlled animal studies, the same relation appears (Tobin and Beard , 1989), that is, trained animals with low iron status had a higher red cell iron turnover (decreased lifetime) than did the non–exercise-trained animals.

The role of iron in human metabolic processes

Iron has several vital functions in the body. It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin, as a transport medium for electrons within cells, and as an integrated part of important enzyme systems in various tissues. The physiology of iron has been extensively reviewed (Dallman, 1986; Kühn, 1996).

Most of the iron in the body is present in the erythrocytes as haemoglobin, a molecule composed of four units, each containing one haeme group and one protein chain. The structure of haemoglobin allows it to be fully loaded with oxygen in the lungs and partially unloaded in the tissues. The iron-containing oxygen storage protein in the muscles, myoglobin, is similar in structure to haemoglobin but has only one haeme unit and one globin chain. Several iron-containing enzymes, the cytochromes, also have one haeme group and one globin protein chain. These enzymes act as electron carriers within the cell and their structures do not permit reversible loading and unloading of oxygen. Their role in the oxidative metabolism is to transfer energy within the cell and specifically in the mitochondria. Other key

functions for the iron-containing enzymes include the synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; and signal controlling in some neurotransmitters, such as the dopamine and serotonin systems in the brain. Iron is reversibly stored within the liver as ferritin and hemosiderin whereas it is transported between different compartments in the body by the protein transferring Dallman, 1986; Kühn, 1996).

Iron requirements

Basal iron losses

Iron is not actively excreted from the body in urine or in the intestines. Iron is only lost with cells from the skin and the interior surfaces of the body - intestines, urinary tract, and airways. The total amount lost is estimated at 14 µg/kg body weight/day (Green, 1968). In children, it is probably more correct to relate these losses to body surface. A non-menstruating 55-kg woman loses about 0.8 mg Fe/day and a 70-kg man loses about 1 mg. The range of individual variation has been estimated to be ±15 percent (FAO/WHO, 1988).

Earlier studies suggested that sweat iron losses could be considerable, especially in a hot, humid climate. However, new studies which took extensive precautions to avoid the interference of contamination of iron from the skin during the collection of total body sweat have shown that these sweat iron losses are negligible (Brune, 1986).

Growth

The newborn term infant has an iron content of about 250-300 mg (75 mg/kg body weight). During the first 2 months of life, haemoglobin concentration falls because of the improved oxygen situation in the newborn infant compared with the intrauterine foetus. This leads to a considerable redistribution of iron from catabolised erythrocytes to iron stores. This iron will cover the needs of the term infant during the first 4-6 months of life and is why iron requirements during this period can be provided by human milk that contains very little iron. Because of the marked supply of iron to the foetus during the last trimester of pregnancy, the iron situation is much less favourable in the premature and low-birth-weight infant than in the term infant. An extra supply of iron is therefore needed in these infants even during the first 6 months of life.

In the full-term infant, iron requirements will rise markedly after age 4-6 months and amount to about 0.7-0.9 mg/day during the remaining part of the first year. These requirements are therefore very high, especially in relation to body size and energy intake (European Communities, 1993).

In the weaning period, the iron requirements in relation to energy intake are the highest of the lifespan except for the last trimester of pregnancy, when iron requirements to a large extent have to be covered from the iron stores of the mother. The rapidly growing weaning infant has no iron stores and has to rely on dietary iron. It is possible to meet these high requirements if the diet has a consistently high content of meat and foods rich in ascorbic acid. In most developed countries today, infant cereal products are the staple foods for that period of life. Commercial products are regularly fortified with iron and ascorbic acid, and they are usually

given together with fruit juices and solid foods containing meat, fish, and vegetables. The fortification of cereal products with iron and ascorbic acid is important in meeting the high dietary needs, especially considering the importance of optimal iron nutrition during this phase of brain development.

Iron requirements are also very high in adolescents, particularly during the period of rapid growth. Girls usually have their growth spurt before menarche, but growth is not finished at that time. Their total iron requirements are therefore considerable. In boys during puberty there is a marked increase in haemoglobin mass and concentration, further increasing iron requirements to a level above the average iron requirements in menstruating women (Rossander-Hulthén and Hallberg, 1996).

Iron absorption

With respect to the mechanism of absorption, there are two kinds of dietary iron: haeme iron and non-heme iron (Hallberg, 1981). In the human diet the primary sources of haeme iron are the haemoglobin and myoglobin from consumption of meat, poultry, and fish whereas non-haeme iron is obtained from cereals, pulses, legumes, fruits, and vegetables. The average absorption of haeme iron from meat-containing meals is about 25 percent (Hallberg, 1981). The absorption of haeme iron can vary from about 40 percent during iron deficiency to about 10 percent during iron repletion (Hallberg *et al.,* 1997). Haeme iron can be degraded and converted to non-haeme iron if foods are cooked at a high temperature for too long. Calcium is the only dietary factor that negatively influences the absorption of haeme iron and does so to the same extent that it influences non-haeme iron (Hallberg, 1993).

Factors influencing dietary iron absorption

Non-haeme iron is the main form of dietary iron. The absorption of non-haeme iron is influenced by individual iron status and by several factors in the diet. Iron compounds used for the fortification of foods will only be partially available for absorption. Once iron is dissolved, its absorption from fortificants and food contaminants is influenced by the same factors as the iron native to the food substance (Hallberg, 1974; Hallberg, 1985). Iron originating from the soil is sometimes present in considerable amounts on the surface of foods as a contaminant originating from dust on air-dried foods or from water used in irrigation. Even if the fraction of iron that is available is often small, contamination iron may still be nutritionally important because of the great amounts present (Hallberg, L. and Björn-Rasmussen, 1981; Hallberg, 1983).

Reducing substances (i.e., substances that keep iron in the ferrous form) must be present for iron to be absorbed (*28*). The presence of meat, poultry, and fish in the diet enhance iron absorption. Other foods contain factors (ligands) that strongly bind ferrous ions that subsequently inhibit absorption. Examples are phytates and certain iron-binding polyphenols (Wollenberg, and Rummel, 1987).

Inhibition of iron absorption

Phytates are found in all kinds of grains, seeds, nuts, vegetables, roots, and fruits. Chemically, phytates are inositol hexaphosphate salts and are a storage form of phosphates and minerals. Other phosphates have not been shown to inhibit non-heme

iron absorption. In North American and European diets, about 90 percent of phytates originate from cereals. Phytates strongly inhibit iron absorption in a dose-dependent fashion and even small amounts of phytates have a marked effect (Gillooly, 1983; Hallberg *et al.,* 1989).

Bran has a high content of phytate and strongly inhibits iron absorption. Whole-wheat flour, therefore, has a much higher content of phytates than does white wheat flour (Hallberg *et al.,* 1987). In bread some of the phytates in bran are degraded during the fermentation of the dough. Fermentation for a couple of days (sourdough fermentation) can therefore almost completely degrade the phytate and increase the bio-availability of iron in bread made from whole-wheat flour (Brune, 1992). Oats strongly inhibit iron absorption because of their high phytate content that results from native phytase in oats being destroyed by the normal heat process used to avoid rancidity (Rossander-Hulthén *et al.,* 1990). Sufficient amounts of ascorbic acid can counteract this inhibition. By contrast, non-phytate-containing dietary fibre components have almost no influence on iron absorption (Siegenberg, 1991).

Almost all plants contain phenolic compounds as part of their defense system against insects, animals, and humans. Only some of the phenolic compounds (mainly those containing galloyl groups) seem to be responsible for the inhibition of iron absorption (Brune *et al.,* 1989). Tea, coffee, and cocoa are common plant products that contain iron-binding polyphenols (Morck *et al.,* 1983). Many vegetables, especially green leafy vegetables (e.g., spinach), and herbs and spices (e.g., oregano) contain appreciable amounts of galloyl groups, that strongly inhibit iron absorption.

Consumption of betel leaves, common in areas of Asia, also has a marked negative effect on iron absorption.

Calcium, consumed as a salt or in dairy products interferes significantly with the absorption of both haeme and non-haeme iron Gleerup *et al.,* 1993). Because calcium and iron are both essential nutrients, calcium cannot be considered to be an inhibitor in the same way as phytates or phenolic compounds. The practical solution for this competition is to increase iron intake, increase its bio-availability, or avoid the intake of foods rich in calcium and foods rich in iron at the same meal (Gleerup, 1995).

The mechanism of action for absorption inhibition is unknown, but the balance of evidence strongly suggest that the inhibition is located within the mucosal cell itself at the common final transfer step for haeme and non-haeme iron. Recent analyses of the dose-effect relationship show that no inhibition is seen from the first 40 mg of calcium in a meal. A sigmoid relationship is then seen, reaching a 60 percent maximal inhibition of iron absorption by 300-600 mg calcium. The form of this curve suggests a one-site competitive binding of iron and calcium. This relationship explains some of the seemingly conflicting results obtained in studies on the interaction between calcium and iron (Hallberg,, 1998).

Enhancement of iron absorption

Ascorbic acid is the most potent enhancer of non-heme iron absorption (Hallberg *et al.,* 1986). Synthetic vitamin C increases the absorption of iron to the same extent as

the native ascorbic acid in fruits, vegetables, and juices. The effect of ascorbic acid on iron absorption is so marked and essential that this effect could be considered as one of vitamin C's physiologic roles (Hallberg *et al.,* 1987). Each meal should preferably contain at least 25 mg of ascorbic acid and possibly more if the meal contains many inhibitors of iron absorption. Therefore, a requirement of ascorbic acid for iron absorption should be taken into account when establishing the requirements for vitamin C that are set only to prevent vitamin C deficiency.

Meat, fish, and seafood all promote the absorption of non-heme iron *(*Björn-Rasmussen and Hallberg, 1979). The mechanism for this effect has not been determined. It should be pointed out that meat also enhances the absorption of haeme iron to about the same extent. Meat promotes iron nutrition in two ways: it stimulates the absorption of both haeme and non-haeme iron and it provides the well-absorbed haeme iron. Epidemiologically, the intake of meat has been found to be associated with a lower prevalence of iron deficiency (Obeagu *et al.,* 2021; Obeagu *et al.,* 2019; Ifeanyi *et al.,* 2020).

Organic acids, such as citric acid, have in some studies been found to enhance the absorption of non-haeme iron. This effect is not observed as consistently as is the effect of ascorbic acid. Sauerkraut (Hallberg and Rossander, 1982) and other fermented vegetables and even some fermented soy sauces enhance iron absorption. The nature of this enhancement has not yet been determined (Macfarlane, 1990).

Conclusion

It was revealed the interleukin 6 and iron levels were raised in the volleyball players after playing due to inflammation of the muscles. Interleukin 6 and iron should be monitored in those palying volleyball.

References

Azevedo, J.L.Jr, Willis, W.T., Turcotte, L.P., Rovner, A.S., Dallman, P.R. and Brooks, G.A. (1989). Reciprocal changes of muscle oxidases and liver enzymes with recovery from iron deficiency. *American Journal of Physiology*. **256**:E401–E405.

Barton, B.E. (1997). IL-6: Insights into novel biological activities. *Journal of Clinical Immunology and Immunopathology Research.* **85**:16-20.

Bjorn-Rasmussen, E., Hallberg, L., Isaksson, B. and Arvidsson, B. (1974). Food iron absorption in man. Application of the two-pool extrinsic tag method to measure heme and non-heme iron absorption. *Journal of Clinical Investigation*. **53**:247–55.

Björn-Rasmussen, E. and Hallberg, L. 1979. Effect of animal proteins on the absorption of food iron in man. *Nutrition and Metabolism.* **23**: 192-202.

Bothwell, T.H., Charlton, R.W., Cook, J.B. and Finch, C.A. (1979). Iron metabolism in man.Oxford, United Kingdom: *Blackwell Scientific*.

Bourque, S.P., Pate, R.R. and Branch, J.D. (1997). Twelve weeks of endurance exercise training does not affect iron status measures in women. *Journal* of the *American Dietetic Association*.10:1116–1121.

Brigham, D.E., Beard, J.L., Krimmel, R. and Kenney, W.L. (1993). Changes in iron status during a competitive season in college female swimmers. *Nutrition*. **9**:418–422.

Brune, M., Rossander, L. and Hallberg, L. 1989. Iron absorption and phenolic compounds: importance of different phenolic structures. *Europen Journal of Clinical Nutrition.* **43**: 547-558.

Brune, M. 1992. Iron absorption from bread in Humans: Inhibiting effects of cereal fiber, phytate and inositol phosphates with different numbers of phosphate groups. *Journal of Nutrition.* **122**: 442-449.

Brune, M. 1986. Iron losses in sweat. *American Journal of Clinical Nutrition.* **43**: 438-443.

Bruunsgaard, H., Galbo, H., Halkjaer-Kristensen, J., Johansen, T.L., MacLean, D.A. and Pedersen, B.K. (1997). Exercise-induced increase in interleukin-6 is related to muscle damage. *Journal of Physiology.* 499:833-841.

Carpenter, C.E. and Mahoney, A.W. (1992). Contributions of heme and nonheme iron to human nutrition. *Critical Reviews* in *Food Science* and *Nutrition.* 31:333–367.

Conrad, M.E. (1993). Regulation of iron absorption. In: PrasadAS., ed. Essential and toxic trace elements in human disease: an update.2nd ed. New York: Wiley-Liss. 43–59

Cook, J.D., Dassenko, S.A. and Lynch, S.R. (1991). Assessment of the role of nonheme-iron availability in iron balance . *American Journal of Clinical Nutrition*. **54**: 717–722.

Dallman, P.R. 1986. Biochemical basis for the manifestations of iron deficiency.

Annual Review of Nutrition. **6:** 13-40.

Dallman, P.R.(1982). Manifestations of iron deficiency. Seminars in *Hematology*.**19**:19–30.

Davis, C.D., Malecki, E.A. and Greger, J.L. (1992). Interactions among dietary manganese, heme iron, and nonheme iron in women. American Journal of Clinical Nutrition. 56:926–32.

DeMaeyer, E. and Adiels-Tegman, M. (1985). The prevalence of anemia in the world. *World health statistics* Q. **38**:302–316.

DeRijk, R.H., Boelen, A., Tilders, F.J. and Berkenbosch, F. (1994). Induction of plasma interleukin-6 by circulating adrenaline in the rat. *Psychoneuroendocrinology.* 19:155- 163.

Dinarello, C.A. (1992). Role of interleukin-1 in infectious diseases. *Immunological Reviews.* 127.

Ehn, L., Carlmark, B. and Hoglund, S. (1980). Iron status in athletes involved in intense physical activity. Medicine *and* Science *in* Sports *and* Exercise.12:61–64.

Estrela, A.L., Zaparte, A., Da Silva, J.D., Moreira, J.C., Turner, J.E., Bauer, M.E. (2017). High volume exercise training in older athletes influences inflammatory and redox responses to acute exercise. *Journal of Aging and Physical Activity*. 25(4):559–569.

European Communities. 1993. *Nutrient and energy intakes for the European*

Community. *EG-Report*. Brussels Luxembourg: Commission of the European Communities.

FAO/WHO. 1988. *Requirements of vitamin A, iron, folate and vitamin B12. Report*

of a Joint FAO/WHO Expert Consultation.. Rome: FAO (FAO Food and Nutrition Series No. 23).

Finch, C.A. and Huebers, M.D. (1982). Perspectives in iron metabolism. *New England Journal of Medicine.* **25**:1520–1525.

Gleerup, A. **(**1995). Iron absorption from the whole diet: comparison of the effect of two different distributions of daily calcium intake. *American Journal of Clinical Nutrition.* **61**: 97-104.

Gleerup, A., Rossander-Hultén, L. and Hallberg, L. (1993). Duration of the inhibitory effect of calcium on non-haem iron absorption in man. *European Journal of Clinical Nutrition.* **47**: 875-879.

Green, R. 1968. Body iron excretion in man. A colloborative study. *American Journal of Medicine.* **45**: 336-353.

Gross, R., Schultnik, W. and Juliawati, H. (1994). Treatment of anaemia with weekly iron supplementation. *Lancet* **344**:821.

Hallberg, L. (1981). Bio-available nutrient density: a new concept applied in the interpretation of food iron absorption data. *American Journal of Clinical Nutrition.* **34**: 2242-2247.

Hallberg, L. (1981). Bio-availability of dietary iron in man. *Annual Review of Nutrition.* 1: 123-147.

Hallberg, L. **(**1979). Dietary heme iron absorption. A discussion of possible

mechanisms for the absorption-promoting effect of meat and for the regulation of iron absorption. *Scandinavian Journal of Gastroenterology*, **14**: 769-779.

Hallberg, L., Hulthén, L. and Gramatkovski, E. (1997). Iron absorption from the whole diet in men: how effective is the regulation of iron absorption? *American Journal of Clinical Nutrition.* **66**: 347-56.

Hallberg, L. **(**1993). Inhibition of haem-iron absorption in man by calcium. *British Journal of Nutrition.* **69**:533-540.

Hallberg, L. (1974). The pool concept in food iron absorption and some of its implications. *Proceedings of the Nutrition Society*. **33**: 285-291.

Hallberg, L. 1985. Factors influencing the efficacy of iron fortification and the selection of fortification vehicles. In: Clydesdale FM, Wiemer KL, eds. *Iron fortification of foods.* New York: Academic Press Inc. pp. 17-28.

Hallberg, L. and Björn-Rasmussen, E. (1981). Measurement of iron absorption from meals contaminated with iron. *American Journal of Clinical Nutrition*. **34**: 2808-2815.

Hallberg, L. **(**1983). Iron absorption from some Asian meals containing contamination iron. *American Journal of Clinical Nutrition*. **37**:272-277.

Hallberg, L., Brune, M. and Rossander, L. (1989). Iron absorption in man: ascorbic acid and dose-dependent inhibition by phytate. *American Journal of Clinical Nutrition.* **49**: 140-144.

Hallberg, L., Rossander, L. and Skånberg, A-B. (1987). Phytates and the inhibitory

effect of bran on iron absorption in man. *American Journal of Clinical Nutrition*. **45**: 988-996.

Hallberg, L. (1998). Does calcium interfere with iron absorption? *American Journal of Clinical Nutrition*. **68**: 3-4.

Hallberg, L., Brune, M. and Rossander, L. (1986). Effect of ascorbic acid on iron absorption from different types of meals. Studies with ascorbic-acid-rich foods and synthetic ascorbic acid given in different amounts with different meals. *Human nutrition. Applied nutrition*. **40:** 97-113.

Hallberg, L., Brune, M. and Rossander-Hultén, L-S. (1987). Is there a physiological role of vitamin C in iron absorption? *Annals of the New York Academy of Sciences*. **498**: 324-332.

Hallberg, L. and Rossander, L. (1982). Absorption of iron from Western-type lunch and dinner meals. *Am. J. Clin. Nutr.*, **35**: 502-509.

Hallberg, L. and Hulthén, L. 1996. Methods to study dietary iron absorption in man -. an overview. In: Hallberg L, Asp N-G, eds. *Iron nutrition in health and disease*. pp. 81-95. London, John Libbey & Company Ltd.

Hallberg, L., Rossander, T., Hulten, L., Brune, M. and Gleerup, A. (1993). Inhibition of haem-iron absorption in man by calcium. *British Journal of Nutrition*.69:533–540.

Hallberg, L., Brune, M., Erlandsson, M., Sandberg ,A.S.and Rossander-Hulten, L. (1992). Calcium and iron absorption: mechanism of action and nutritional importance. *European Journal of Clinical Nutrition*. 46:317–27.

Ifeanyi, O. E., Uzoma, O. G., Amaeze, A. A., Ijego, A. E., Felix, C. E., Ngozi, A.

F., Nchekwubedi, C. S., & Chinenye, K. S. (2020). Maternal Expressions (Serum Levels) of Alpha Tumour Necrosis Factor, Interleukin 10, Interleukin 6 and Interleukin 4 in Malaria Infected Pregnant Women Based on Parity in a Tertiary Hospital in Southeast, Nigeria. *Journal of Pharmaceutical Research International*, ***32***(23), 35-41.

Jonsdottir, I., Schjerling, P., Ostrowski, K., Asp, S., Richter, E.A. and Pedersen, B.K. (2000). Muscle contractions induces interleukin-6 mRNA production in rat skeletal muscles. *Journal of Physiology.* **528**:157-163.

Kang, S., Narazaki, M., Metwally, H. and Kishimoto, T. (2020). Historical overview of the interleukin-6 family cytokine. *Journal of Experimental Medicine.* **217**(5):4.

Kanemaki, T., Kitade, H., Kaibori, M. , Sakitani, K., Hiramatsu, Y., Kamiyama, Y., Ito, S. and Okumura, T.(1998). Interleukin 1beta and interleukin 6, but not tumor necrosis factor alpha, inhibit insulin-stimulated glycogen synthesis in rat hepatocytes. *Hepatology.* **27**:1296-1303.

Klausen, T., Richalet, J.P., Olsen, N.V. and Pedersen, B.K. (1997). Hypoxemia increases serum interleukin-6 in humans. *European Journal of Applied Physiology*. **76**:480-482.

Kühn, L.C. 1996. Control of cellular iron transport and storage at the molecular

level. In: Hallberg LA, et al., eds. *Iron nutrition in health and disease.* p. 17-29. London, John Libbey and Company.

Lyle, R.M., Weaver, C.M., Sedlock, D.A., Rajaram, S., Martin, B. and Melby, C.L.(1992). Iron status in exercising women: the effect of oral iron therapy vs increased consumption of muscle foods. *American Journal of Clinical Nutrition* **56**:1049–1055.

MacIntyre, D.L., Sorichter, S., Mair, J., Berg, A. and McKenzie, D.C. (2001).

Markers of inflammation and myofibrillar proteins following eccentric exercise in humans. *European Journal of Applied Physiology*. **84**:180-186.

Macfarlane, B.J. 1990. The effect of traditional oriental soy products on iron absorption. *American Journal of Clinical Nutrition*. 51: 873-80.

Mastorakos, G., Chrousos, G.P. and Weber, J.S. (1993). Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *Journal of Clinical Endocrinology and Metabolism*. 77:1690-1694.

Mattcs, C.A. (1999). Interactions of adrenaline and TNF and IL-6 in the control of lipolysis from adipocytes around lymph nodes. *Cytokine*. **11**:334-346.

Morck, T.A., Lynch, S.E. and Cook, J.D. 1983. Inhibition of food iron absorption by coffee. *American Journal of Clinical Nutrition*. **37**: 416-420

Nehlsen Cannarella, S.L., Fagoaga, O.R., Nieman, D.C., Henson, D.A., Butterworth, D.E. Schmitt, R.L., Bailey, E.M., Warren, B.J. Utter, A. and Davis, J.M. (1997). Carbohydrate and the cytokine response to 2.5 h of running. *Journal of Applied Physiology*. **82**:1662-1667.

Newhouse, I.J., Clement, D.B., Taunton, J.E. and McKenzie, D.C. (1989). The effects of prelatent and latent iron deficiency on physical work capacity. *Medicine* and *Science* in *Sports* and *Exercise*.**21**:263–268.

Newhouse, I.J., Clement, D.B. and Lai, C. (1993). The effects of iron supplementation and discontinuation on serum copper, zinc, calcium, and magnesium levels in women. *Medicine* and *Science* in *Sports* and *Exercise*.**25**:562–571.

Nielsen, H.B., Secher, N. and Perdersen, B.K. (1996). Lymphocytes and NK cell activity during repeated bouts of maximal exercise. *American Journal of Physiology*. **271**:R222-R227.

Nielsen, P. and Nachtigall, D. (1998). Iron supplementation in athletes. Current recommendations. *Sports Medicine*.4:207–216.

Northoff, H., and Berg, A. (1991). Immunologic mediators as parameters of the reaction to strenuous exercise. *International Journal of Sports Medicine*. **12**:S9-15.

Obeagu, E.I., Vincent, C.C.N. and Chinedu-Madu, J.U. (2019). Studies on some cytokines of apparently healthy Nigerian women aged 10-40 years. *International Journal of Current Research in Medical Sciences*. **5**(12): 24-30

Ostrowski, K., Hermann, C., Bangash, A., Schjerling, P., Nielsen, J.N. and Pedersen, B.K. (1998).A trauma-like elevation in plasma cytokines in humans in response to treadmill running. *Journal of Physiology*. **508**:949-953.

Ostrowski, K., Rohde, T., Asp, S., Schjerling, P. and Pedersen, B.K. (1999). The cytokine balance and strenuous exercise: TNF-alpha, IL-2beta, IL-6, IL-1ra, sTNF-r1, sTNF-r2, and IL-10. *Journal of Physiology*. **515**:287-291.

Ostrowski, K., Rohde, T., Zacho, M., Asp, S. and Pedersen, B.K. (1998). Evidence that IL-6 is produced in skeletal muscle during intense long-term muscle activity. *Journal of Physiology*. **508**:949-953.

Pedersen, B.K., Ostrowski, K., Rohde, T. and Bruunsgaard, H. (1998). The cytokine response to strenuous exercise. *Canadian Journal of Physiology and Pharmacology*. **76**:505-511.

Pedersen, B.K., and Hoffman- Goetz, L. (2000). Exercise and the immune system: regulation, integration and adaption. *Physiological Reviews* **80**:1055-1081.

Pedersen, B.K., Steensberg, A., Fischer, C. (2004). The metabolic role of IL-6

produced during exercise: is IL-6 an exercise factor? *Proceedings of the Nutrition Society*. **63**(2):263–267.

Radomski, M.W., Sabiston, B.H.and Isoard, P. (1980). Development of "sports anemia" in physically fit men after daily sustained submaximal exercise. *Aviation, Space,* and *Environmental Medicine*. **51**:41–45.

Rossander-Hulthén, L., Gleerup, A. and Hallberg, L. 1990. Inhibitory effect of oat products on non-haem iron absorption in man. *European Journal of Clinical Nutrition.* 44: 783-791.

Seligman, P.A., Caskey, J.H., Frazier, J.L., Zucker, R.M., Podell, E.R.and Allen, R.H. (1983). Measurements of iron absorption from prenatal multivitamin-mineral supplements. *Obstetrics* and *Gynecology*.61:356–62.

Siegel, A.J., Hennekens, C.H., Solomon, H.S. and Van Boeckel, B.V.(1979). Exercise-related hematuria: findings in a group of marathon runners. *Journal of the American Medical Association*.241:391–392.

Siegenberg, D. 1991. Ascorbic acid prevents the dose-dependent inhibitory effects of polyphenols and phytates on nonheme-iron absorption. *American Journal of Clinical Nutrition.* 53: 537-41.

Solvell, L. (1996). Oral iron therapy—side effects. In: Hallberg L., ed. Iron deficiency: pathogenesis, clinical aspects, therapy. London: *Academic Press*. 573–583

Stewart, J.G., Ahlquist, D.A., McGillD, B., Ilstrup, D.M., Schwartz, S.and Owen, R.A. (1984). Gastrointestinal blood loss and anemia in runners. *Annals of Internal Medicine*.**100**:843–845.

Stouthard, J.M., Romijn, J.A., van der, P.T., Endert, E., Klein, S., Bakker, P.J.,

Veenhof, C.H. and Sauerwein, H.P. (1995). Endocrinologic and metabolic effects of interleukin-6 in humans. *American Journal of Physiology*. **268**:E813-E819.

Testa, M., De Ruvo, E., Russo, A., Citterio, F., Serino, F., Mangoni, A., Capogrossi, M.C. and Sperti, G. (2000). Induction of interleukin-1beta and interleukin-6 gene expression in hypoperfused skeletal muscle of patients with peripheral arterial disease. *Italian Heart Journal*. **1**:64-67.

Tsigos, C., Papanicolaou, D.A., Kyrou, I., Defensor, R., Mitsiadis, C.S. and Chrousos, G.P. (1997). Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. *Journal of Clinical Endocrinology and Metabolism.* **82**:4167-4170.

Tobin, B. and Beard, J.L. (1996). Iron and exercise. In: Wolinsky I, Driskell JA., eds. CRC handbook of sports nutrition: vitamins and trace minerals. *Boca Raton, FL: CRC Press*. 137–156

Viteri, F.E. (1995). Iron deficiency in children: new possibilities for its control. *International Child Health*.**6**:49–61.

Weaver, C.M. and Rajaram, S. (1992). Exercise and iron status. *Journal of Nutrition*.122:782–787.

Wijn, J.F., De Jongste ,J.L., Mosterd, W.and Willebrand, D. (1971). Hemoglobin, packed cell volume, and iron binding capacity of selected athletes during training. Nutrition and Metabolism.**13**:129–139.

Xing, Z., Gauldie, J., Cox, G., Baumann, H., Jordana, M., Lei, X.F. and Achong, M.K. (1998). IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *Journal of Clinical Investigation.* **101**:311-320.

Gillooly, M. 1983. The effect of organic acids, phytates and polyphenols on absorption of iron from vegetables. *British Journal of Nutrition*. **49**: 331-342.

Nielsen, P. and Nachtigall, D. (1998). Iron supplementation in athletes. Current recommendations. *Sports Medicine*.4:207–216.

Obeagu, E. I., Amedu, G. O., Okoroiwu, I. L., Okafor, C. J., Okun, O., Ochiabuto, O. M. T. B., & Ukeekwe, C. O. (2021). Evaluation of Plasma Levels of Interleukin 6 and Iron Status of Football Players in a Nigerian University. *Journal of Pharmaceutical Research International*, *33*(59B), 383-388. https://doi.org/10.9734/jpri/2021/v33i59B34393

Obeagu, E.I., Vincent, C.C.N. and Chinedu-Madu, J.U. (2019). Studies on some cytokines of apparently healthy Nigerian women aged 10-40 years. International Journal of Current Research in Medical Sciences.;5(12):24-30

Ifeanyi, O.E., Uzoma, O.G., Amaeze, A.A., Ijego, A.E., Felix, C.E., Ngozi, A.F., Nchekwubedi, C.S. and Chinenye, K.S. (2020). Maternal Expressions (Serum Levels) of Alpha Tumour Necrosis Factor, Interleukin 10, Interleukin 6 and Interleukin 4 in Malaria Infected Pregnant Women Based on Parity in a Tertiary Hospital in Southeast, Nigeria. Journal of Pharmaceutical Research International. 32(23):35-41.