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RESEARCH ARTICLE

THE PHYSIOLOGY OF NUTRITION IN HAEMATOLOGY.

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Abstract

Blood plays a role in maintaining homeostasis where various haematological processes take place to ensure the normal functioning of blood and its components in response to physiologic changes. Adequate nutrition significantly influences the outcomes of blood-related processes and may either promote or threaten health. At the cellular level, vitamins, minerals and calories are needed in metabolic activities which ensure the normal formation and functioning of blood cells. Deficiencies and toxicities result in acute and chronic conditions brought about by diminished blood functioning. These require clinical management through drug therapy, dietary changes and patient education.

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The Physiology of Nutrition in Haematology

The blood is made up of a liquid matrix called plasma wherein different cells and fragments of cells, referred to as formed elements, are dissolved and suspended (Tortora & Derrickson, 2008). Platelets and red and white blood cells compose the formed elements. The many functions of blood involve transport, regulation and protection. Firstly, it transports oxygen and nutrients from the lungs and gastrointestinal tract to all body cells. It carries carbon dioxide, heat and metabolic wastes from the cells to the body organs responsible for eliminating them. It further carries hormones from their endocrine sources to the target cells.

Secondly, it regulates the pH of body fluids using buffer mechanisms and also causes the normalization of body temperature. It maintains the water content of cells by exerting osmotic pressure via the action of proteins and ions. Lastly, it performs protective functions through blood coagulation and immune responses. The blood cannot perform its homeostatic functions without enough nutrients and calories. Insufficient and excessive amounts lead to medical conditions threatening bodily functions and survival. This paper discusses the physiology of nutrients and calories in haematological processes, the pathologies related to nutrient deficiencies and toxicities, and the management of these conditions.

Vitamins, Minerals and Haematologic Processes:-

Several vitamins and minerals are indispensable to normal blood formation and function. These are iron, copper, calcium, cobalt, zinc, and vitamins A (retinol), C (ascorbic acid), E (tocopherol), K (phylloquinone) as well as the B vitamins folate, B2 (riboflavin), B6 (pyridoxine) and B12 (cyanocobalamin) (Tortora & Derrickson, 2008; Butensky, Harmatz & Lubin, 2008; Munoz, Villar & Garcia-Erce, 2009). As inorganic elements, trace minerals are mainly derived from diet. Some, such as iron and calcium, can be stored in body organs. Most vitamins are also obtained through dietary intake with the exception of vitamin K which is synthesized by gut bacteria. Sufficient amounts of nutrients enable blood coagulation, haematopoiesis and immunological functioning.

Nutrients and Blood Coagulation

Calcium and vitamin K play a role in the clotting function of platelets. In the event of blood vessel injury causing bleeding, platelets adhere to the area of the break while signalling other platelets to join them. The aggregation of platelets forms a plug over the break and releases substances which activate coagulation pathways (Tortora & Derrickson, 2008). Fibrin, a protein, is the end product and it forms a mesh over RBCs and platelets to form a clot which is more stable than a plug. Vitamin K is indispensable in the synthesis of procoagulation factors II, VII, IX and X (Greer, et al., 2009). The role of calcium is to bridge the different steps of the coagulation pathways to enable clot formation. When injury involves tissues outside blood vessels, factor III (thromboplastin) is released which requires calcium in order to stimulate factor X that, together with factor V, produces an enzyme called prothrombinase in the extrinsic coagulation pathway (Greer, et al., 2009).

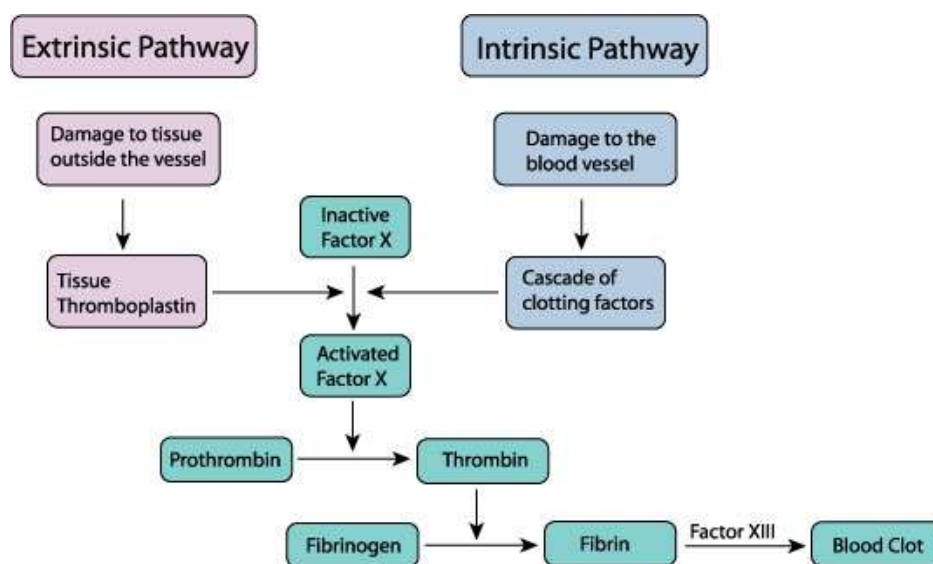


Figure 1:- Intrinsic and Extrinsic Coagulation Pathways

Alternatively, injury within a blood vessel leads to exposure of underlying collagen fibres, an event that activates factor XII which, in turn, activates factor X only in the presence of calcium (Greer, et al., 2009). The latter again combines with factor V to generate prothrombinase in the intrinsic coagulation pathway. No matter the initial pathway taken to produce prothrombinase, the enzyme goes through a pathway common to both with calcium acting as catalyst in the conversion of factor II (prothrombin) into thrombin (Greer, et al., 2009). Calcium is again a requisite for thrombin to convert fibrinogen into a fibrin network over the plug. Thrombin activates factor XIII which lends stability to the network, thus forming a clot.

Nutrients and Haematopoiesis

Cobalt, copper, iron, vitamin A, and the B vitamins folate and B12 are useful in erythropoiesis, the production of RBCs, and in haematopoiesis or the synthesis of all formed elements in particular. In haematopoiesis, but more importantly in erythropoiesis, vitamin B12 acts as a coenzyme in the conversion of folate from its inactive methyl form into its tetrahydrate active form which is necessary for DNA formation (Hustad et al., 2002). An adequate supply of both B12 and folate result in RBCs whose rates of DNA synthesis are adequate and timely enough to keep pace with the rapid cell division taking place in the bone marrow in response to an increase in physiologic demands (Elliott, 2008).

Zinc, vitamin E and phosphorus are other nutrients that play a role in haematopoietic DNA and RNA synthesis (Tortora & Derrickson, 2008). On the other hand, vitamin B2 is transformed into cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) which facilitate vitamin metabolism including that of its fellow B12 vitamins folate, B6 and B12, thus rendering them useful not only in DNA synthesis but also in hemoglobin production (Hustad et al., 2002). RBCs produced in the presence of sufficient and well-metabolized vitamins, especially folate and B12, have mature nuclei in conjunction with similarly mature cell cytoplasm and RNAs. As such, they are able to assume the normal morphological appearance and physiological functions of a normal RBC.

Iron is an element of cytochrome which plays a role in mitochondrial respiration. The mineral is also necessary in the production of metabolic enzymes, the transcription of RNA, and the synthesis of DNA (Smith, 2003). It is a chief component not only of RBC haemoglobin, as will be discussed in the next section, but of all highly proliferative cells and is indispensable in the generation and differentiation of WBCs (Anderson & MacLaren, 2011). For this reason, white blood cells actively compete with other cells for the acquisition of iron, especially when supply is inadequate. When anaemia develops, the proliferation and differentiation of WBCs decrease. Vitamin A also aids in haematopoiesis, positively affecting the differentiation of RBC, WBCs and platelet progenitor cells (Smith, 2003).

Normal erythropoietic functioning is indicated by circulating RBCs whose number is sufficient to fulfil oxygenation functions (Butensky, Harmatz & Lubin, 2008). Erythropoiesis is stimulated by the hormone erythropoietin secreted by the kidney. In turn, the production of erythropoietin is induced by hypoxia-inducible factor (HIF), a renal protein synthesized during hypoxic events (Elliott, 2008). Once adequate oxygenation is achieved, the enzyme prolyl hydroxylase (PH) deactivates HIF which effectively halts the negative-feedback process of RBC synthesis.

Cobalt is a component of vitamin B12 and is known to bind to the protein or globin portion of hemoglobin (Hodges et al., 2007; Simonsen et al., 2011). It is a strong potentiator of erythropoiesis because of its capacity to inhibit the PH enzyme leading to the accumulation of HIF (Qui et al., 2012). For this reason, the use of this trace mineral as a doping method has been explored by athletes seeking ways to enhance their oxygenation capabilities (Lippi, Franchini & Guidi, 2005). However, copper not only affects RBCs but also WBCs and platelets. Although the exact mechanism is unclear in WBCs, studies show that copper enables the self-regeneration and differentiation CD34(+) precursor cells in the bone marrow (Lazarchick, 2012). For yet unknown reasons also, the presence of copper is associated with normal thrombopoiesis.

Nutrients and Haemoglobin Synthesis

The ability of RBCs to transport oxygen is made possible by haemoglobin which is formed by a heme and a globin. Vitamin B6 functions as a co-enzyme to a wide array of other enzymes involved in amino acid metabolism, one of which is δ -aminolevulinic acid (ALA) synthase (Hustad et al., 2002). This enzyme is specific to RBC precursor cells and is a catalyst of the crucial step that ensures heme synthesis during the production of haemoglobin (Hunter & Ferreira, 2011). The creation of heme occurs intracellularly, taking place first in the mitochondria and then in cytosol, producing a ring-like molecule known as coproporphyrinogen III (Pittman, 2011).

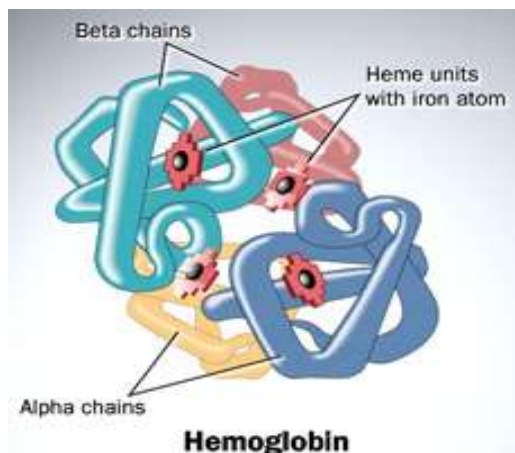


Figure 2:- Structure of a Haemoglobin Molecule

Upon return to the mitochondrion, this molecule becomes protoporphyrin IX. Ferrochelatase, an enzyme, incorporates one atom of iron into the porphyrin ring so that one unit of functional heme is produced (Pittman, 2011). Copper plays a role in the final phase of heme synthesis. The mineral is a component of cytochrome C oxidase, a mitochondrial enzyme which aids in the conversion of iron from an inactive ferric form to an active ferrous state (Mullally, Vogelsang & Moliterno, 2004). This allows the atom to become attached to the porphyrin ring by ferrochelatase.

On the other hand, globin consists of two alpha chains and two beta chains connected by four nitrogen atoms. The

heme units are enveloped inside the four chains which provide them protection. When RBCs go through the pulmonary artery, haemoglobin-oxygen encounters result in oxygen lodging between the lone iron in heme and the nitrogen atom in the globin (Pittman, 2011). One atom of iron is present in one heme unit and one heme unit is enclosed in each of the four globin chains to form one haemoglobin molecule (Hemoglobin, 2009). For this reason, one molecule of haemoglobin has the capacity to transport four oxygen molecules.

Nutrients and Iron Transport, Mobilization and Storage

Following oral intake, iron is either utilized or stored as ferritin by cells in the G.I. tract. Stored ferritin would later be eliminated in stool once the G.I. epithelium sloughs off and is renewed. Alternatively, iron can bind to the protein apotransferrin to form transferrin for subsequent transport to plasma so that it can be used by bone marrow in the formation of haemoglobin or stored for future use in the liver (Petrak & Vyoral, 2005). This process is made possible by the ferroxidase hephaestin, another protein, which is synthesized during iron-deficient states. Hephaestin is made up in part by copper (Petrak & Vyoral, 2005).

Iron and vitamin A deficiencies often co-exist in nutritional surveys of human populations as validated in a study of preschool children in the Republic of the Marshall Islands (Palafox et al., 2003). For this reason, vitamin A is deemed a contributory factor to anaemia. One explanation is that vitamin A plays a significant role in the release of iron stored in liver cells. This hypothesis has been validated through an animal experiment conducted by Jiang et al. (2012). In rats treated with diets low in or without vitamin A, messenger ribonucleic acids (mRNA) regulating the proteins involved in the storage and release of iron stores was noted to increase (Jiang et al., 2012). These proteins are transferrin receptors and ferritin. The mRNA is modulated by iron regulatory protein 2 (IRP2) in the event of low iron levels.

Ferritin facilitates the intracellular storage of iron and its level was increased in the absence of vitamin A (Jiang et al., 2012). The emphasis on iron storage during avitaminosis A is corroborated by rising concentrations of iron in both rat liver and spleen. The normal response would have been a decrease in ferritin, and thereby iron storage, and an increase in iron export from liver cell to plasma through the transport functions of transferrin. This would ensure a greater availability of serum iron for use in erythropoiesis. From plasma, transferrin receptors on bone marrow cells facilitate iron uptake. In the rat model, however, transferrin receptors were noted to decrease in terms of sensitivity without vitamin A (Jiang et al., 2012). As such, cells could not effectively take in and use iron. The results of the study validate previous findings that insufficient amounts or the lack of vitamin A inhibits the release of iron from hepatic storage and prevents its active utilization for erythropoiesis.

Nutrients and Immunological Functioning

Specific to WBCs or lymphocytes, zinc promotes normal hormonal thymulin activity in the thymus which allows T lymphocytes to mature (Mullally, Vogelsang & Moliterno, 2004). Moreover, it regulates helper T cell 1 and helper T cell 2 activity in order for these to promote normal immunological responses to infection. Finally, zinc modulates the programmed cell death or apoptosis of lymphocytes and also an adequate supply of their progenitor cells to ensure WBC production and replacement (Mullally, Vogelsang & Moliterno, 2004). In addition, vitamin B6 helps B lymphocytes in the formation of antibodies or immunoglobulins, while adequate amounts of vitamin C assist in their effective functioning (Tortora & Derrickson, 2008).

Calories and Haematologic Processes:-

In addition, calories also play a role in haematological processes. Haematopoiesis relies on a steady supply of hematopoietic stem cells (HSCs) which actively self-regenerate during their period of quiescence and to differentiate during periods of activation (Gan et al, 2010). During differentiation, HSCs proliferate and transform into progenitor cells, further mature and become fully functional blood cells ensuring normal physical development and survival especially during periods of acute physiologic stress. The capacity for a high rate of

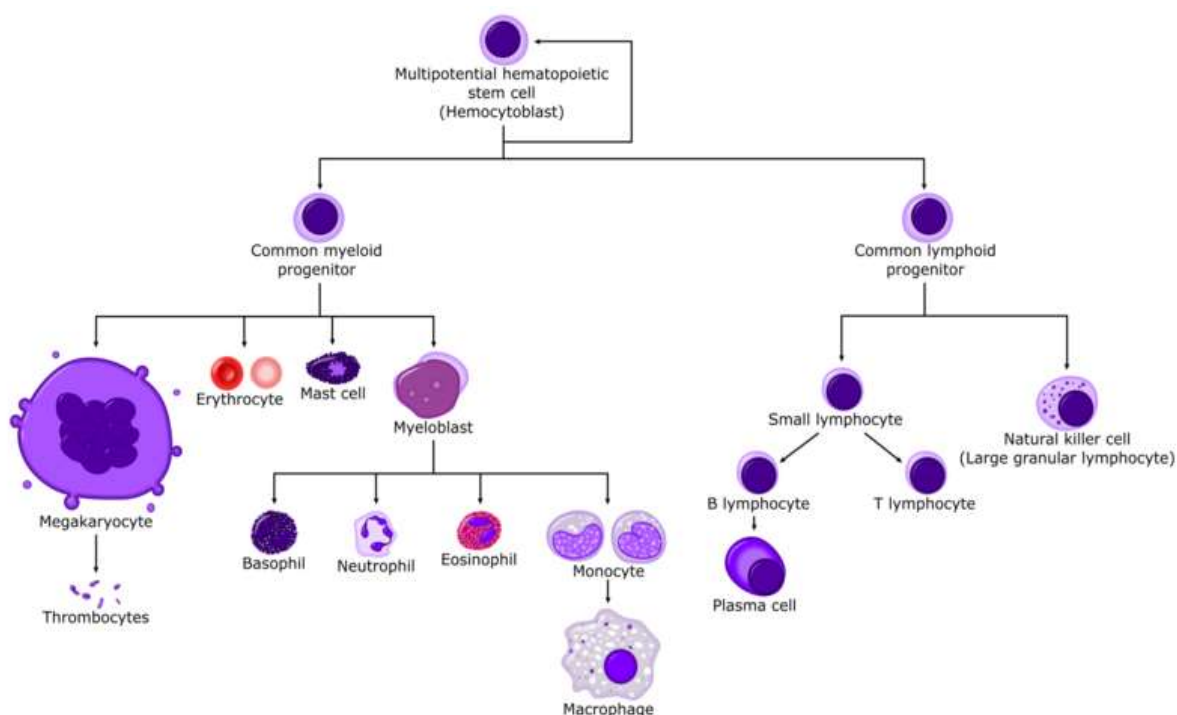


Figure 3:- Hematopoietic Stem Cell Proliferation and Differentiation

self-regeneration, proliferation and differentiation allows the bone marrow to continually replenish the required number of RBCs which only last an average of 120 days and produce an average of five trillion of these cells needed throughout a person's lifetime, a value which can further increase in the event of blood and iron loss (Gan et al, 2010). Proliferation also allows the maintenance of an adequate platelet count, and supports the ability of WBCs to multiply and produce immunoglobulins when infections develop.

Haematopoietic processes then require high levels of energy to sustain their equally high rate of energy metabolism consisting of both catabolism for energy production and anabolism for cell synthesis. HSCs in a quiescent phase have a lesser number of mitochondria. Hence, these mainly rely on glycolysis or the anaerobic breakdown of carbohydrates into glucose and then to adenosine triphosphate (ATP) for cellular energy, a metabolic process resulting in a net ATP production of just 2 mol for each mol of glucose used (Suda, Takubo & Semenza, 2011). On the other hand, differentiating HSCs develop more mitochondria permitting the utilization of oxidative phosphorylation, the aerobic pathway, which can produce a net ATP amounting to 36 mol for every mol of glucose (Suda, Takubo & Semenza, 2011).

The use of either the aerobic or anaerobic means of energy metabolism corresponds to cellular needs in specific phases of HSCs. Regeneration requires less ATP compared to the processes of proliferation and differentiation. Besides glucose catabolism, however, HSC proliferation also relies on a supply of precursor molecules necessary for the synthesis of lipids, amino acids and nucleotides through the tricarboxylic acid (TCA) cycle, also called the Krebs cycle (Suda, Takubo & Semenza, 2011). Therefore, meeting nutritional requirements for carbohydrates, proteins and fats is a requirement for the fulfillment of hematopoietic processes.

Iron Physiology and Iron Traffic:-

The specific functions of iron in haematopoiesis and blood cell functioning have been described above. These specifically concern DNA and RNA synthesis, metabolism, oxygen transport, and cell proliferation as well as differentiation. However, its absorption, transport, storage and loss in the body, referred to as iron traffic, need to be elucidated in terms of the two forms of iron - heme and non-heme (Hentze, Muckenthaler & Andrews, 2004). Heme

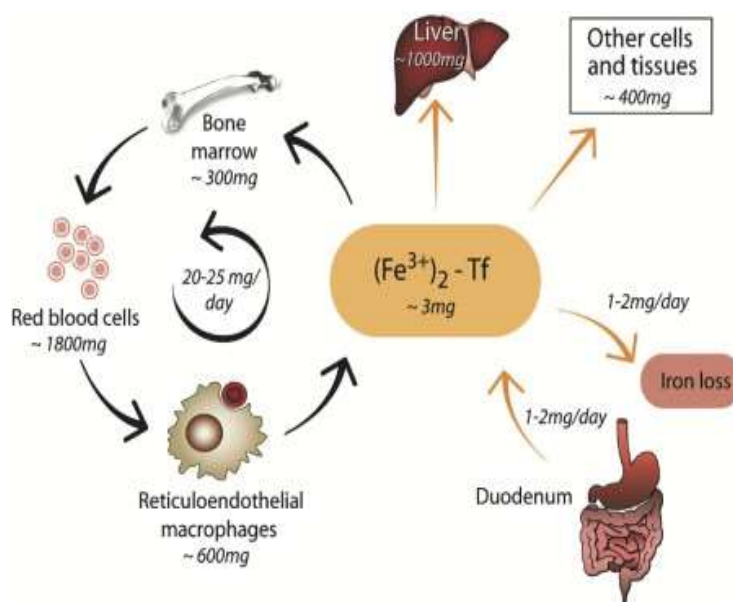


Figure 4:- Iron Traffic: Absorption, Transport, Storage and Loss

iron is the product of the phagocytisation and recycling of old and damaged RBCs. This is accomplished by macrophages, specifically those that are part of the reticuloendothelial system (RES) (Wang & Pantopoulos, 2011). Iron from this route is directly stored in the cytosol of macrophages. On the other hand, non-heme iron is that which passes through the G.I. system from oral intake. The absorption of heme iron, as discussed above, occurs in intestinal cells. Transport to the plasma, and subsequently to cells and proteins in need of iron, from the G.I. tract occurs through apotransferrin/transferrin.

Besides those currently used by cytochromes, enzymes, haemoglobin in RBCs and myoglobin in muscle cells, iron goes to storage not only in macrophages but also in bone marrow and the liver (Munoz, Villar & Garcia-Erce, 2009; Butenksy, Harmatz & Lubin, 2008). However, a small portion of iron is lost from the epithelial sloughing of the G.I. tract and during menses. When iron levels are low, storage sites utilize ferroportin, a protein, as

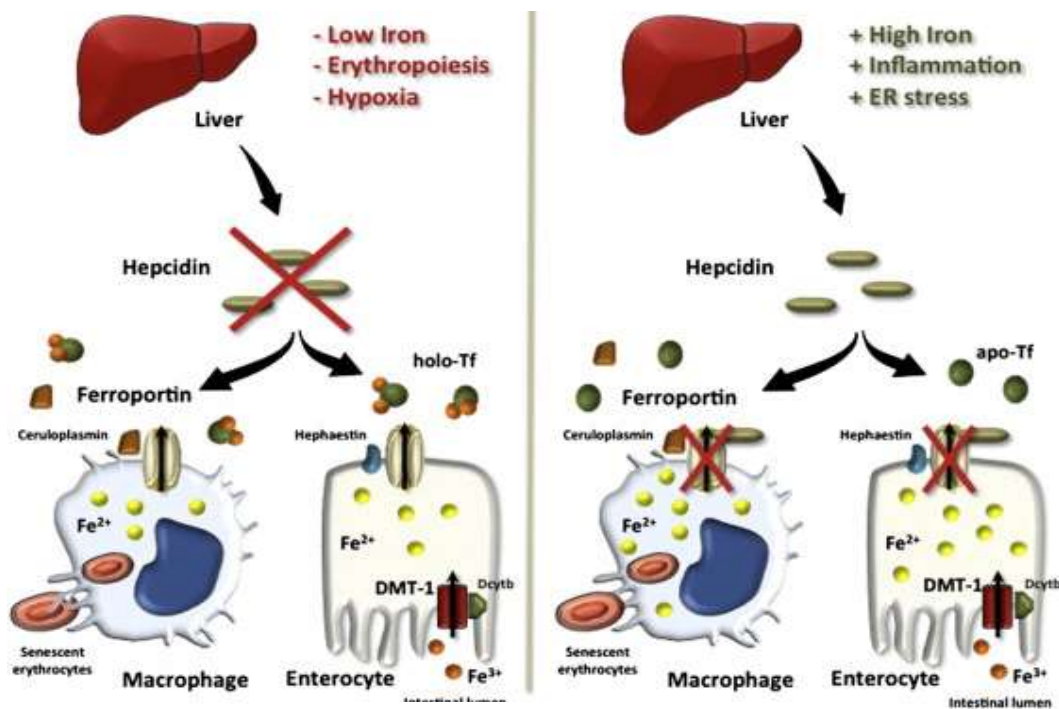


Figure 5:- Iron Homeostasis Mediated by Hepcidin

the mechanism by which iron is exported from cells so that it can be transported by the apotransferrin/transferrin mechanism. Hepcidin is a peptide which is the primary regulator of iron homeostasis (Lin et al., 2007). When iron levels are low, it enables ferroportin to transport iron extracellularly from storage sites to the circulation via transferrin. However, hepcidin inhibits ferroportin when transferrin levels are high causing iron to remain stored intracellularly in its ferritin form (Hentze, Muckenthaler & Andrews, 2004).

Nutrient Deficiencies and Anaemia:-

The roles of nutrients in key haematological processes are fulfilled only when these are in sufficient amounts. Deficiencies result in pathologies, such as various types of anaemias, whose signs and symptoms are related to the inhibition of the particular nutrient's functions. The most common pathology is iron-deficiency anaemia (IDA). It results from poor dietary iron intake, impaired absorption associated with illnesses of the G.I. tract, excessive loss due to bleeding, or increase in need beyond the normal such as during pregnancy (Tortora & Derrickson, 2008). IDA can also be secondary to vitamin A deficiency which inhibits the release of stored iron for biological utilization (Jiang et al., 2012). Further, low copper levels slow down the transformation of inactive iron to its active form so that less iron is ready for transport to cells (Auclair et al., 2005).

Since iron is important in cellular metabolism and DNA synthesis, normal haemopoiesis, and erythropoiesis in particular, is hampered. This leads to decreased RBC proliferation and differentiation despite increased physiologic demand. Further, RBCs assume a microcytic and hypochromic appearance because of impaired haemoglobin synthesis in the absence of iron (Tortora & Derrickson, 2008). With a lower than normal RBC count and similarly low haemoglobin levels, there is insufficient oxygenation at the cellular level. A state of hypoxia occurs and manifests as pallor, fatigue, dizziness, shortness of breath, headaches and anorexia (Tortora & Derrickson, 2008). Subsequently, the normal development of body systems, especially in the unborn and growing children, is hindered. IDA is associated with slower rates or stunted growth. It is also linked to lower IQs and decreased capacities for learning (Harper, 2012). The heart may compensate with increased cardiac work load in an effort to enhance oxygenation but with primary defects in the blood's oxygen transport capacity, hypoxia persists. If left unmanaged, death may occur.

Another type of nutrition-related pathology is megaloblastic anaemia which stems from an inadequate vitamin B12 and folate supply in the body. This can be primary, again because of insufficient dietary intake, or secondary due to the body's inability to absorb the vitamin in the gut, e.g. as a result of the side effects of chemotherapeutic medications. These B vitamins are also requisites for DNA synthesis and similar to IDA, low levels slow down RBC synthesis (Butenksy, Harmatz & Lubin, 2008). As a consequence, structural defects in the RBC nucleus contribute to cell dysfunction.

In normal RBC, the nucleus is ejected extracellularly prior to cell transport from the bone marrow to plasma. In megaloblastic anaemia, the RBC maintains a large, immature nucleus which does not eject. As such, the RBC is unable to assume a biconcave appearance where this structure increases the oxygen-carrying capacity of the cell (Tortora & Derrickson, 2008). For this reason, RBCs in megaloblastic anaemia have a limited capacity for iron transport while at the same time, less than the needed number of RBCs is produced. A state of hypoxia occurs with symptoms similar to those of IDA. In extreme deficiency, platelets and WBCs are affected as well leading to both thrombocytopenia and leukopenia (Butenksy, Harmatz & Lubin, 2008).

The third type of pathology related to nutrition is pernicious anaemia whose etiology involves vitamin B12. The absorption of this vitamin occurs in the G.I. tract and is facilitated by gut bacteria and intrinsic factor produced by gastric parietal cells (Butenksy, Harmatz & Lubin, 2008). Genetic conditions wherein intrinsic factors are not expressed, as well as conditions or diseases of the stomach and colon which diminish intrinsic factor production and vitamin absorption, limit B12 availability in the circulation. Without B12, there is again slowed DNA formation in RBCs resulting in low RBC and haemoglobin supply in plasma (Butenksy, Harmatz & Lubin, 2008).

Insufficiency in iron, copper, cobalt, phosphorus, vitamin A and the B vitamins involved in haematological processes lead to inhibited proliferation and differentiation of haematopoietic stem cells in general (Hustad et al., 2002). Severe zinc and vitamin C deficiency lead to poor immune functioning (Mullally, Vogelsang & Moliterno, 2004). Finally, inadequate vitamin K precipitates haemorrhagic disease as blood clotting is inhibited by the inactivity of vitamin-K dependent coagulation factors (Hallberg et al., 2001). Regarding, calories, inadequate carbohydrate, fat and protein intake inhibits haematopoiesis and restricts normal cell functioning leading to

impairments in the physiologic processes that these cells control (Gan et al., 2010).

Management and Treatment of Nutrient Deficiencies:-

The main treatment and management of nutrient deficiencies is through supplementation and diet modification. The latter can be accomplished by adopting a more judiciously planned diet incorporating foods that are rich in the nutrient or nutrients where deficiencies are noted. Most trace elements, such as copper, zinc and cobalt, can be obtained in most foods including meat, fish, eggs and dairy (Tortora & Derrickson, 2008). Vitamin B12 is abundant in meat while the other B vitamins, along with vitamin K, can be sourced from vegetables and fruits. Lean meats, liver, dark green and leafy vegetables, and fortified cereal or bread are high-iron foods recommended for persons who are considering blood donation (Suggestions for the blood donor, n.d.).

Alternatively, treatment with the pure form of vitamins and minerals can be given especially in severe deficiency. Vitamin K can be administered orally, intravenously or through the intramuscular and subcutaneous routes (Martin, 2008). B complex multivitamins are available over the counter while B12 can be given as injections for pernicious anaemia where the oral route is ineffective. Zinc is available in either liquid, capsule or tablet form. Iron can also be given as injections, intravenous infusions or by mouth in either liquid or tablet form (Butenksy, Harmatz & Lubin, 2008). Similar to pharmacologic treatment, vitamin and mineral administration must follow protocols aiming to ensure correct drug, correct route and correct dose.

How each nutrient is absorbed in the body must also be taken into consideration during administration. Care must also be taken in preventing interactions between the different nutrients as these can inactivate one or the other if inappropriately administered together. Iron inhibits vitamin E absorption and it is recommended that the latter be corrected first prior to initiating supplementation with the former (Butenksy, Harmatz & Lubin, 2008). This is because vitamin E can be corrected within a shorter span of time compared to iron deficiency which takes from two to four months of continuous treatment for haemoglobin levels to normalize. Vitamin C enhances the absorption of iron and both should be given together (Suggestions for the blood donor, n.d.). Further, efficient iron absorption is facilitated by a low gastric pH and hence it should be taken in between meals (Doyle, 2009). The use of concurrent antacids is contraindicated during iron therapy.

Nutrient Toxicities and Related Pathologies:-

Nutrient toxicities result in chronic conditions which significantly reduce quality of life. Though there is a marked decline in the incidence of nutrient toxicities, particularly hypervitaminosis, compared to a decade ago, cases still occur today. The decline in incidence is due to the stricter regulation of vitamins in health care settings. As such, most events of toxicity today are attributed to overconsumption of dietary supplements (Sauvant et al., 2012). The most notable toxicity involves iron and vitamin A, both of which are stored primarily in the liver and which can cause significant damage to the organ when in excess. Diet-related iron toxicity is mainly due to excessive exogenous supplementation especially when combined with a high-iron diet. For example, a person on a diet composed mainly of animal meat rich in iron who also takes in dietary supplements with high iron content, usually without benefit of medical advice, would be at high risk for iron toxicity. In the case of iron overload among Africans in the Sub-Saharan region, however, the cause is increased dietary intake of iron from the consumption of alcoholic beverages fermented in the traditional way in steel drums (Gujja et al., 2010).

Although hepcidin is able to regulate iron homeostasis, the body's inability to dispose of excess amounts of the nutrient poses a limitation on mechanisms to maintain balance in states of toxicity. As mentioned earlier, hepcidin inhibits ferroportin expression, and therefore iron export from cells to the circulation, when iron levels are high (Hentze, Muckenthaler & Andrews, 2004). Transferrin then works to transport excess iron from plasma to cells for storage. Ferritin inside cells binds to and deactivates iron to prevent intracellular oxidative damage. However, in levels of toxicity, transferrin eventually becomes saturated and cannot bind all the iron for transport (Siah, Trinder & Olynyk, 2005). Similarly, there is a limit to the amount of ferritin that cells can accumulate.

The liver is the main repository of the mineral and as it accumulates greater amounts of transferrin-bound iron, non-transferrin bound iron in plasma find their way to other organs, namely the heart, pituitary gland, bone marrow, pancreas, spleen and the central nervous system (Gujja et al., 2010). Progressive organ damage from excessive iron occurs because the mineral initiates hydrogen peroxide transformation into a free-radical state (Quieroz-Andrade et al., 2009). Hydrolytic enzymes are then activated which initiate the damage and death of cells. Antioxidant enzymes and antioxidants such as vitamin C have been noted to be ineffective in preventing cellular damage which involves

the mitochondria, DNA, cellular proteins and the cell membrane (Eaton & Quian, 2002; Kikuchi et al., 2012).

In the liver, injury from the oxidants produced by iron can lead to hepatoma or cirrhosis where lesions in the liver have been noted in imaging studies of individuals experiencing iron overload (Quiroz-Andrade et al., 2009). Damage to the beta cells of the pancreas interferes with insulin production and for this reason iron toxicity can predispose individuals to secondary diabetes mellitus (Eaton & Quian, 2002). In the heart, iron overload causes cardiomyopathy (Gujja et al., 2010). Deposition of iron in the ventricles can cause arrhythmias while irreparable damage in the conduction system would require the placement of a pacemaker.

On the other hand, hypervitaminosis A has a tendency to manifest as a subacute or chronic condition which means that amounts way above RDA levels have been taken for long periods of time (Sauvant et al., 2012). However, in acute states such as in the one-time administration of the vitamin in megadoses among infants, bulging fontanelles, as a sign of increased intracranial pressure from cerebral oedema, are common manifestations (Mahalanabis et al., 1997). In adults, common signs and symptoms of acute toxicity include headache, nausea, vomiting and drowsiness suggesting CNS involvement, as well as fever, anorexia, papilledema and changes in skin colour (Nagai et al., 1999). Pain in bones and joints are also common complaints.

Vitamin A is absorbed in the G.I. tract, converted to retinol ester and then transported by chylomicrons, a type of lipoprotein, into the circulation so that it can be taken up by hepatic stellate cells for storage or use (Penniston & Tanumihardjo, 2006). When vitamin A is needed elsewhere, retinols in the liver bind to retinol-binding proteins (RBP) and exported into the circulation for cellular uptake. During chronic toxicity, liver cells and RBPs cannot store and transport, respectively, any more retinol. The unbound retinols combine instead with lipoproteins in the blood and cause damage to target cells.

Retinols not bound to RBPs enhance the free-radical degradation of cellular lipids and proteins in peroxidation and carbonylation processes respectively, eventually resulting in cell dysfunction (Dalle-Donne et al., 2006; de Oliveira & Moreira, 2007). Vitamin A mediated oxidative stress, or the rise of free radicals in the body, is thought to accelerate the progression of acute and chronic conditions and has been shown to promote the breakdown of bone increasing the risk for osteoporosis (Fahmy & Soliman, 2009). Animal experiments also show that vitamin A targets the mitochondria of the cerebellum and cortex of the brain (de Oliveira & Moreira, 2007). Similar to iron toxicity, hypervitaminosis A also induces hepatic damage leading to cirrhosis.

Management and Treatment of Nutrient Toxicities:-

It is important to manage nutrient toxicities to ensure survival. Whichever the treatment modality recommended, obtaining a diet-related patient history is essential in identifying the etiology of excess nutrient levels. Patient education must be done to address them. If diet is the etiology, advice on diet changes should be given, and if diet supplements are the cause, these must be stopped immediately. With regards to vitamin A toxicity, this is the sole management (Johnson, 2007; Dugdale, 2012). Supportive treatment must also be given for acute signs and symptoms of toxicity. Finally, the patient must be evaluated for nutrient-induced damage to body organs to facilitate treatment and management.

Chelation therapy is the main treatment of iron toxicity which involves removing toxic non-transferrin bound iron (NTBI) from the circulation through urinary excretion. There are three classes of chelating drugs: deferoxamine, deferiprone and deferasirox (Hershko, 2010). Deferoxamine, which is administered through subcutaneous infusion, has been the first to be developed and as such, its efficacy is well established (Shander & Sazama, 2010). Its main advantage over newer drugs is its capacity to facilitate iron elimination through bile. On the other hand, deferiprone has the capacity to enter cells and promote the removal of excess iron within them while also exerts a stronger protective effect on cardiac tissues compared to deferoxamine. Finally, the oral drug deferasirox is the newest and has superior NTBI clearance rates in plasma based on clinical trial results (Hershko, 2010).

Compliance is also essential and should be emphasized as noncompliance has been identified as a major factor in treatment failure (Ault & Jones, 2009). Monitoring of iron and blood values should also be done as basis for treatment cessation. Further, chelating drugs have notable side effects and require frequent assessment during the course of treatment. Deferoxamine can damage the eyes, ears and nerves so that current guidelines include routine eye examination and audiometric testing (Shander & Sazama, 2010). Agranulocytosis and neutropenia can occur with deferiprone treatment requiring complete blood counts and WBC differentials on a weekly basis. Meanwhile,

deferasirox has a potential for kidney damage and monitoring through monthly renal function tests is needed. Prevention of these serious side effects through monitoring and prompt management leads to better outcomes.

Conclusion:-

Vitamins and minerals are indispensable in fundamental haematological processes such as oxygen transport, blood coagulation and antibody synthesis and functioning. These nutrients, along with a sufficient carbohydrate, fat and protein intake, also support stem cell renewal, proliferation and differentiation during erythropoiesis in particular and hematopoiesis in general. These processes promote homeostasis through the production of normal blood cells in adequate numbers meeting the physiologic demands for oxygen and nutrients, clotting factors and immune responses among others especially in the event of trauma, infection and disease. Nutritional deficiencies seriously impair normal blood physiology and must be appropriately managed as these cause pathologic states that reduce the chances of long term survival. Care must be taken to avoid nutrient toxicities which likewise pose serious threats to health.

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