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Review Article

Blood Physiology, Composition, Functions, Components of Plasma in the Blood, Transfusion, Homeostasis and Newest Advances in the Treatment of Blood Disorders: A Review

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Abstract

Being a specialized connective tissue, blood is an important part of the human system as it maintains the homeostasis and supports the life support functions. It consists of elements that have been produced and the plasma. Plasma, the liquid part: The plasma part, and about half of your blood, is: About 55% of it is water, which carries the red blood cells: in it is water, a little of some salts (potassium, sodium, so called because of the elements reactivity), and all the chemicals your body needs, and also the waste products, ammonia and carbon dioxide of which it is made. The rest 45% comprises of materials that have been produced such as red blood cells, white blood cells and platelets. These elements play different and different functions. Red blood cells, such as, transport oxygen through blood capillaries, and inherited deficits of Fibrinogen, Factor (F) II, FV, FX and FXI, FXIII and combined FV and FXIII deficiency (FV +VIII) make up 3-5 percent of all hereditary coagulation deficiencies and are usually family-dominant inherited through autosomal recessive traits; these uncommon bleeding disorders include RBDs. RBDs are most common in various inadequacies of the different genes; e.g. in case of FVII, it is 1 in 500,000 in cases of FXIII, FXI, and FXII, it is approximately 1 in 2 million. Their popularity, however, is in certain regions as high as hemophilia B because of the tradition of consanguinity marriage. The data on how to treat the people with RBDs is lacking, even though the disorders are highly uncommon and may lead to a very wide range of symptoms, including extremely mild ones, yet extremely severe as well. Moreover, an appropriate plan on how to manage them individually cannot be adopted at this stage because of the technological limitation of laboratory testing and because there is no final verdict on how they should be identified. Lastly, various thrombotic incidences were reported, in particular, in deficiencies in fibrinogen, FII, FVII or FXI, although RBDs are associated with bleeding tendency. Therefore, the replacement treatment must be ustomized according to the needs of each patient, considering his or her prothrombotic risk factors and his or her personal or family history of bleeding and thrombosis. 17 The level of antigen should also be considered in fibrinogen and FII deficiency.

Keywords: Blood Physiology, Components of Plasma, Transfusion, Treatment, Blood Disorders

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Introduction

Blood circulatory system of vertebrates such as human beings is a body fluid that transfers oxygen and nutrients to the cells and transfers waste materials to the cells. It is a special liquid in the body and essential energy of life, which occurs in a continuous flow to sustain the functions of the body. In medical terms, blood is a liquid, which is discharged by the heart to all sections of the body and pumped in again. In conclusion, blood flow in the body in both veins and arteries is vital to life. Conversely, blood is a tissue by itself given the fact that it is composed of different types of specialized cells all of which come together to carry out some functions. The blood is a vital fluid that circulates throughout the body and has a number of critical bodily processes[1,2]. The pushing of blood around our bodies by our hearts which supplies the oxygen supply in our bodies happens when we breathe in. The heart redirects the blood to the lungs to enable the blood to store more oxygen. Time after time, such a trend is followed. Human blood consists of four elements namely plasma, white blood cells, red blood cells and platelets. The multi-purpose red blood cells are produced as a matter of the stem cells in the bone marrow that carry the oxygen all over the body and the carbon dioxide is transported back into the lungs. They are a constituent of 44% of blood fluid and are used in many ways. The antigens present on the surface of red blood cells help the immune system to identify the blood type. Although white blood cells make up less than one percent of the body tissue of the human heart, they are very essential in human health and survival. Its only duty is to protect the blood against infection. Platelets are tiny part of blood which is used to prevent bleeding, by making clots in the ruptured blood vessels. They are important in flooring of blood. Plasma is a yellowish fluid, which is transparent, and sticky at times. It transports blood cells throughout the body and it is mainly made up of water and proteins. Plasma is important in the development of blood, as it helps in the transportation of cells and other things (nutrients, hormones, waste products, etc.) in the body. Blood is a fluid that is perceived to be a connective tissue in some occasions; its classification can be changed and this can vary according to the beliefs and practices that one holds. Blood occupies about seven to eight percent of your body weight. The two main components in it are plasma and formed elements. The liquid element is plasma, and it transports most of the elements, such as proteins, electrolytes, hormones, and wastes. The components that are manufactured are used to do specific functions. The body has been designed to carry oxygen to the body tissues through the oxygen carrying red blood cells, white blood cells that act as protectors and platelets that carry out the function of blood clotting. The bulk of blood cells in higher animals[345] are red and have a role to play in the distribution of breathing gasses. The immunity is handled by white blood cells and platelets are concerned with blood clotting and healing. The other description is that red blood cells contain the primary reason as to why blood is red in color. The blood supplies oxygen to all our tissues and organs, distributes fluids all through the body, contain pH buffer. It also shields us against diseases and infections which are harmful. The body responds fast when there is internal and external changes. Moreover, the most illustrative case of how other organs may be subjected to pathology as a result of blood problems, is the example of human leprosy, since the kidney may also have problems with its blood circulation. This is beneficial to programs of health promotion, disease prevention, as well as early diagnosis.

The Blood's Composition

The plasma and the rest of the substances that constitute blood is a form of connective tissue. Plasma is a straw-colored liquid that is formed as components of blood cells as well as clotting factors. Blood plasma, which is a liquid part of the blood, consists of hydrogen, electrolytes, nutrients, hormones, proteins, and waste products. Water, which is a solvent of the movement of different compounds in the organism, contains 90 to 92% of plasma. The rest (8-10 percent) consists of nutritions, waste products, electrolytes, hormones, enzymes, and plasma proteins. Plasma contains certain proteins that are central to it.

Albumin controls the osmotic pressure of the body and carries drugs and hormones. The glocalbins play role in transport and immune system. Protein fibrinogen -Plays a key role in coagulating blood. Electrolytes such as bicarbonate, sodium, potassium and calcium regulate osmotic balance, neuro-muscular activity and pH. Hormones secreted by endocrine glands and intestinal-absorbed nutrients are also carried by plasma. The excretion of waste products, including urea and creatinine is done by the kidneys.

Plasma and Hematological Fluids

The plasma of blood is a liquid that comprises about 55 percent of the blood. It is a liquid that carries many chemicals in the body; it is of a yellowish hue of a mild shade and it is majorly composed of water (90% to 92%). In the rest of the 8-10 percent of plasma, there is the proteins, electrolytes, minerals, hormones, enzymes and waste products. Albumin, the most common plasma protein, helps in maintenance of the osmotic pressure and transport of fatty acids, hormones and pharmaceuticals. Two of the most significant functions of globulins are the immunological response and transport of lipids and vitamins, and the process of blood clotting and wound healing is the work of fibrinogen[6]. Electrolytes that regulate the amount of water in the body and the operation of the nerves and muscles include salt, bicarbonate, potassium, calcium, magnesium, chloride, and the pH of the blood.

Hemocyte Cells

The most numerous components of blood are the red blood cells (RBCs) or erythrocytes, and they carry the majority of oxygen and carbon dioxide in the organism. It is because of its roughly 250 million haemoglobin molecules that a red blood cell can carry oxygen to the tissues and excrete carbon dioxide. The secretion of the erythropoietin hormone by the kidney controls the process of the erythropoiesis that leads to the production of red blood cells in the red bone marrow. The life of red blood cells is approximated to be a hundred years. The presence of iron-containing protein hemoglobin, which is able to bind oxygen, can fit more easily into their biconcave form due to the augmented surface area to engage in efficient gas exchange, and the absence of a nucleus or organelles. With an average of 250 million molecules of hemoglobin, the red blood cells can transport oxygen to the tissues and carbon dioxide to the lungs in order to be exhaled. The red bone marrow produces the red blood cell (RBC) and the secretion of the hormone erythropoietin, which is primarily secreted by the kidney, regulates this process. Macrophages in the liver and spleen destroy and break down the red blood cells after an average of 120 days. Some of the hemoglobin constituents are shed off, but the iron is recycled[7,8,9]. The red colour of blood is due to the high level of hemoglobin that exists in these cells. Anemia or polycythemia problems with the number of red blood cells (RBC) can have extensive implications on the metabolic and overall health. The body requires sufficient oxygen to its tissues, and to achieve this, a normal number of RBCs is required.

CD4+ T Expressions

Leukocytes or white blood cells are very essential in the defense mechanism of the immune system against the pathogens, foreign substances, and abnormal cells. When they are produced in the bone marrow, they are always on the alert to threats since they pass in the lymphatic and the circulatory systems. The leukocytes can be further distinguished into two broad categories, as the granulocytes and the agranulocytes. Some of the cells that are classified under granulocytes are neutrophils, eosinophils and basophils basing on the staining capacities of their granules. Most of the white blood cells are neutrophils, which participate in the process of phagocytosis, in which microbes such as bacteria and fungi are enclosed and destroyed. Two different types of the mast cells are the histamine releasing basophils and the parasite fighting eosinophils.

The Distillation of CO_2 and O_2

The key role that blood plays in cellular respiration and homeostasis is the transport of oxygen and carbon dioxide. In red blood cells, Oxygen binds quickly and reversibly to

hemoglobin after entering the lungs and diffusing over the alveolar membrane into blood plasma. Hemoglobin is able to bind oxygen efficiently because it has a high binding affinity of oxygen. Eventually, it is the hemoglobin that transfers approximately 98.5% of oxygen in blood, but only a small amount of oxygen is actually dissolved in plasma. The blood delivers hemoglobin with oxygen that is contained in it to the tissues where it is utilized to generate energy through metabolism. As a matter of fact, a byproduct of aerobic metabolism is a carbon dioxide, which cannot be eliminated in the body unless it is transported back to the lungs by the tissues. Carbonic anhydrase enzyme is involved in the production of carbon dioxide by the red blood cells and approximately 70 percent of it is transported in plasma as a form of bicarbonate ions (HCO3 -). The remaining 80-90 percent of the carbon dioxide is dissolved in plasma whereas the remaining 20-23 percent is carried by carbaminohemoglobin which is also bound in hemoglobin[10,11]. Collectively, blood circulation is an effective exchange mechanism which maintains the acid-base balance of the body through periodical supply of oxygen to the tissues and elimination of carbon dioxide. The two destructive effects that may occur due to the issues with the process of transporting blood are hypoxia (low oxygen) and hypercapnia (high carbon dioxide), which are disastrous to the organs.

Transfusions and Groups of Blood

The blood has a critical role in immunological terms of protecting the body against harmful pathogens, poisons, and aberrant cells. It is primarily the role of white blood cells and their plasma proteins which do this. The immune system depends on the swarm of white blood cells that arrange the quest and annihilation of dangerous microbes in blood and tissues. To give an example, neutrophils are the first line of defense of the immune system against bacterial infection due to their rapid phagocytes ability; eosinophils combat parasites and release allergen causing mediators; and basophils release histamines, and other mediators in response to an inflammatory reaction. The monocytes are transformed to macrophages in the body, which can absorb harmful substances, dead cells, and other immune cells. Adaptive immune responses are based on the lymphocytes, which consist of a number of B cell and T cell types. B cells can produce antibodies and T-cells kill malignant or diseased cells directly. Plasma contains immunoglobulins (antibodies) and complement proteins that are involved in pathogen identification and elimination, phagocytosis and inflammation. Moreover, the cytokines also facilitate the communication of cells (the overwhelming majority of immune cells require the skills of communicating with each other) and help regulate immune reactions (these small signaling molecules circulate in the blood). Due to a multitude of vital cellular and molecular components, blood is an ideal medium in which the immune system can be monitored, provide a rapid response and long-term immunity, which are both required by the body to protect against an ailment and ensure internal health. Blood plays a great role in maintaining homeostasis, a condition of internal stability that is needed to guarantee optimal body functioning. It keeps the balance and the stability through numerous physiological processes. Cellular metabolism plays an important role in body cellular functions since it helps to eliminate carbon dioxide and other waste products of metabolism and provide nutrients and oxygen to body tissues. The red blood cells in the body transmit the heat to the whole body and regulate the quantity of blood that reaches the skin to lose or preserve heat. Bicarbonate buffer is among the numerous blood buffer systems that have a role of maintaining the pH of the blood in the limited range of 7.35 -7.45 by neutralizing overabundance of acids and bases. Electrolytes such as calcium, potassium, and sodium are necessary in the proper functioning of the muscles and nerves and are carried by the blood in order to maintain the body levels of fluids and electrolytes. The immune system is maintained through fighting off invaders by the use of antibodies and white blood cells and prevents excessive bleeding following injuries due to blood clotting mechanisms. Blood is more of a

dynamic media, when it comes to the stability and health of the body, and it is constantly adapting to changes, both internal and external.

Blood Disorder

A blood disease is a medical condition affecting the red blood cells, the white blood cells, the platelets, or plasma, or an amalgamation of all these four elements of blood. The immune system and the circulatory system may be affected by both inherited and acquired types of these disorders. Anemia is a familiar disorder with red blood cells. A low count or shape of the red blood cells hinders the ability of blood to deliver oxygen to the tissues, a symptom of anemia. Anemia can be thalassemia, iron-deficiency and sickle cell anemia. Leukemia is one of the types of cancer that has an impact on white blood cells. Under such a situation, there is overloading of the immune system by errant cells that grow out of control. Two additional white blood cell diseases, which reduce the performance of the immune system, are lymphoma and leukopenia. Reduced number of platelets is referred to as thrombocytopenia. This may result in excessive bleeding. Immune response and antibody production may be affected by disorders of the plasma component; one of them is multiple myeloma. The early diagnosis and intervention of blood disorders is the only way to reduce the symptoms and avoid additional consequences of [12]. The identification of blood diseases requires blood tests; some blood diseases could be treated using medication, transfusion, and a bone marrow transplant.

New Methodologies of Blood Disorders

Although the needs of many patients regarding the particular blood disorders are still not met, many patients have been positively addressed owing to improvement in treatment and reduction in the effects of the disease. This and the following drugs are the new drugs which have just been approved to the regulatory market and have therefore increased access of patients to treatment options where none existed previously: The first treatment of hemolytic anemia in adults with pyruvate kinase deficiency, a debilitating and rare genetic disorder. In the case where there is a genetic mutation in PKKLR gene, red blood cells may lack the required energy. Two of the new CAR-T cell therapies are large B-cell lymphoma and the other individual is relapsed or resistant multiple myeloma. This was the first of its kind to receive a license to be used as therapy in the treatment of a rare form of bone marrow cancer called cytopenic myelofibrosis. Cytopenic myelofibrosis is also a condition of incredibly low levels of blood platelets or thrombocytopenia. Cytopenias are experienced in approximately 66 percent of myelofibrosis patients. With the help of an approved medication, it is now possible to prevent bleeding episodes in patients with a severe form of von Willebrand disease. The initial targeted biologic in sickle cell disease in pain crises (vaso-occlusion)[13]. The drug binds to a protein that mediates cellular interactions which may lead to pain crisis in sickle cell disease patients. The sickle cell disease makes people in the hospital because of the severe pain that refers approximately 200,000 individuals to the emergency room annually in the US. It is the first drug to approach the underlying cause of sickle cell disease which is the injury and sickling of red cells. One of the most important abnormalities in sickle cell disease is the sickle cell hemoglobin polymerization; the drug inhibits the process by enhancing hemoglobin attraction to oxygen.

Blood Clotting Disorders and Genomic Medicine

Gene therapies are still in the development phase, but eventually, patients with genetic defects who have blood problems will be able to enjoy the long-term benefits, although not a cure. Due to this, they imply a significant decrement of the current burden and expenses of treatment.

Hemophilia A

Most hemophilia Factor (FVIII) replacement therapy patients with the gold standard is a permanent therapy in patients, particularly the more severe ones. The use of it may be injected as much as 2-3 times per week, or 100-150 times per year, to prevent severe bleeding, or to maintain joint function. A new preventative treatment

alternative that can be administered by the patient not so frequently has just appeared. The research and development of gene therapy against severe hemophilia is underway. A have shown statistically significant and sustained reductions in bleeding rates and almost complete discontinuation of factor replacement therapy intake during the years after only one treatment delivery.

Hemophilia B

To avoid potentially fatal episodes of bleeding, reduce the number of episodes of joint bleeding, and preserve the joint functioning, individuals with hemophilia B, like hemophilia A, usually require lifelong prophylactic infusion of factor replacement therapy. The common interval of infusion delivery is 100 to 150 times annually or 2-3 times weekly. Some of the newer factor replacement treatment regimens allow the frequency of infusion to be stretched to once every 1-2 weeks. Studies on gene therapies of severe and moderately severe hemophilia B are almost complete. These treatments have shown a significant reduction in bleeding rates and almost obviation of factor replacement therapy years after one treatment.

Factor 8 and 9 and their Action in Clotting

During the propagation phase of the coagulation cascade, FVII and FIX are only the inactive precursors of the two proteins circulating in blood and activated only in case of a hemostatic challenge. On the surface of the activated platelets in the presence of calcium ions and phospholipids, active FX activating complexes are formed, comprising of FVIII and FIX. When three receptors FXa (the enzyme), FX (the substrate) and FVIIIa (the cofactor) are colocalized, the activation of FX and the concomitant generation of sufficient thrombin to achieve hemostasis is 24 million times faster. In the initiation stage of blood coagulation[14,15], a hemophilic patient would normally secrete the minimal amount of thrombin that is required to trigger secondary hemostasis. The propagation phase significantly decreases the thrombin production level which happens during the secondary burst at the absence of either FIX or its cofactor FVIII. The consequences of ineffectiveness of this impairment of the FX activating complex activity are ineffective fibrinolysis and bleeding diatheses.

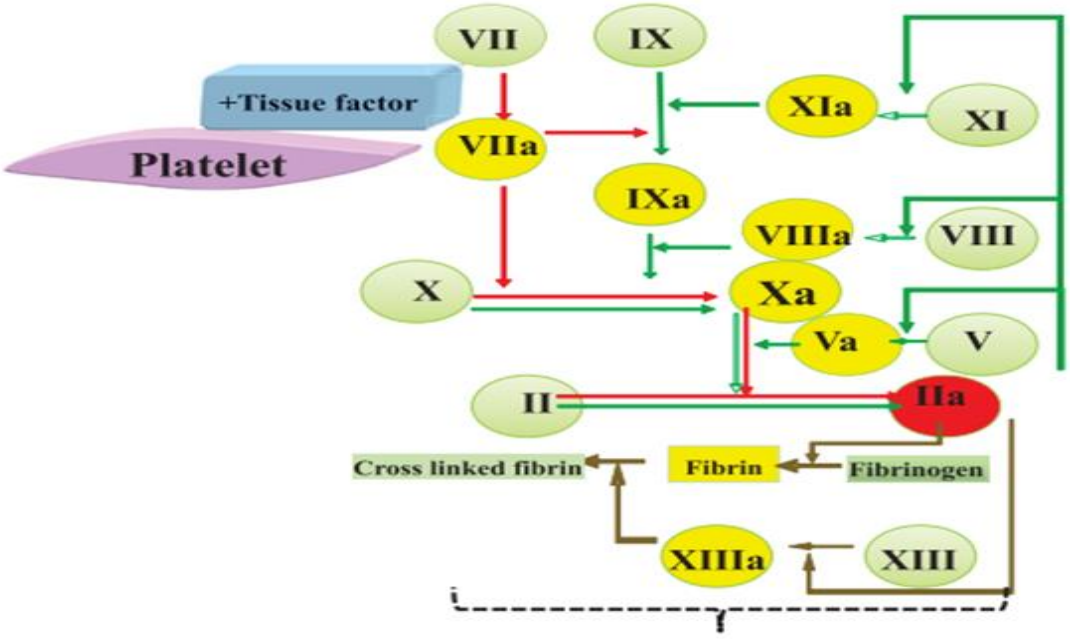

Figure 1: In vivo blood coagulation: when tissue factor, which is attached to a cell membrane, comes into contact with factor (F), the process begins in mammals. Section VII. When FVII is converted to the protease FVIIa, the TF-FVIIa complex activates FIX and FX.

The spontaneous bleeding into muscles and joints (hemarthrosis) is the most frequent symptom of severe hemophilia. The joints show 90 percent of bleeding in hemophilia patients. Knees are the most attacked part (>50 percent of all cases), followed by the elbows, ankles, shoulders, and lastly the wrists. The knees and elbows particularly are weak links since they act as hinge articulations and are therefore susceptible to angular and rotatory forces. The features of hemophilic arthropathy are joint inflammation, hemorrhage, enlarging of the synovium, development of the villous formations, and loss of cartilages and bone. The red blood cell autolysis is the mechanism that results in the development of hemosiderin in synovial tissue after acute intra-articular hemorrhage. This causes a state of inflammation in the form of interleukin-6 [IL-6], interleukin-1b and tumor necrosis factor 2. After only four days, the sub-synovium will be neovascularized, and the existence of villous growth on the synovial surface will be visible. This will cause hypertrophy of the synovium, and thus more brittle will be the joint that is more likely to rebleed even with light load as in falling when you walk or having some little injury. Chronic, persistent inflammatory reaction known as hemophilic synovitis results because of repetitive bleeding. A re-bleeding vicious cycle may result in the formation of a target joint. Though what exactly is happening to give rise to synovial hypertrophy and cell proliferation has been enigmatic, there is an emerging body of evidence that c-myc and mdm2 expression and other key angiogenic molecules such as matrix metalloproteinase-9 and alliteration of vascular endothelial growth factor [VEFG] are involved in this process. Repeated bleeding into the target joint aggravates the proteolysis and bone and cartilage breakdown because the joint capsule is increasingly inflamed, and the synovial fluid has increasing amounts of hydrolytic enzymes like acid phosphatase, cathepsin D, and collagenases.

Molecular genetics Factor VIII

F8 gene is 9 kilobases in length, spans about 186 kilobase pairs, and it is found on the long arm of X-chromosome (Xq. 28) [48]. Having a domain structure of A1-A2-B-A3-C1-C2, FVIII is a large multidomain glycoprotein including 2351 amino acids. Thrombin cleavage inhibits Big B domain in the case of FVIII activation. The normal locations of FVIII production are the liver, kidney and endothelial cells where it is synthesized as an inactive single-chain protein. After thorough post-translational processing, the half-life of the FVIII is about 12 hours once it is discharged into the circulation in adults. During the activation of coagulation cascades, proteinolytic cleavage of FVIII takes place allowing the separation of VWF and the production of biological activity required to engage factor X activating complex. Quickly activated FVIII is deactivated. Owing to the instability of activated FVIII, this may take place via subunit dissociation and also through enzymatic processing using FIXa, FXa, and activated protein C. Moreover, proteins that bind to low-density lipoprotein receptors mediate FVIII catabolism. The prevalence rate of this condition is high (1:5000) due to the high rate of mutation of the F8 gene (2.5 x 10- 5 to 4.2 x 10- 5). The mutation rate is high due to the high size of FVIII gene and frequent occurrence of intron 22 inversion[16,17,18,19]. The intron-22 and intron-1 reversed are possibly caused by the fact that when males are undergoing meiosis, the ends of the X chromosomes are flipped whereas when females are undergoing meiosis, this is prevented by homologous pairing. Nonetheless, large scale deletions are normally caused by recombination which is hastened during female meiosis when x chromosomes are in pairs. The constant replication of male germ cells and the colossal magnitude of the FVIII gene is the principal determinant that implies the rise of point mutations in the F8 gene, which influences approximately half of cases of inversion negative cases. Despite this, a current effort is being put on finding the underlying cause of FVIII deficiency in an estimated 5 percent of hemophilia A cases when a pathogenic mutation in the F8 gene is not identified.

Factor IX

It is located at chromosome X (Xq27) (34 kb) with 8 exons in the F9 gene. Fix is produced in the

liver and is a precofactor with a 57Kda and 462 amino acids. A rough endoplasmic reticulum signal peptidase cleases the first exon containing a signal sequence that ensures hepatocyte release; the second exon contains 29 amino acids and it is the pro-peptide sequence and gla domain. This key post-translational change of the initial 12 glutamic acid residues in the gla domain of the mature polypeptide is done by a vitamin K-dependent 7 -carboxylase, which binds to the pro-peptide using a recognition site. Once these residues have γ carboxylated, a specific peptidase cleaves the pro-protein and the fully formed protein prior to secretion and results in a 415 amino acid zymogen. In regard to high affinity calcium binding, platelets binding and interaction between FIX and its co-factor, FVIIIa, exons 4 and 5 encode epidermal growth factor-like domains[20,21]. Produced by exons 7 and 8, the catalytic domain has the standard catalytic triad of His 221, Asp 269 and Ser 365 and exon 6 produces the activation peptide. The release of factor IX to LRP within the cell surface proteoglycans may be one of the mechanisms involved in the intracellular degradation of activated FIX. Due to spontaneous deamination of 5-methylcytosine, numerous of the mutations that recur in the database are found at the sites with hypermutable dinucleotide matches in the genome, i.e., at cpositions with CpG. A high percentage of mild hemophilia B is covered by very few founder mutations (20-30%). Once an individual attains the adult age, he/she might be in a position to correct some mutations in the F9 gene promoter region independently. This is demonstrated by hemophilia B Leiden which is a mutation that is in constitutive transcription factor start sites with no hormonally regulated androgen response regions in the F9 promoter.

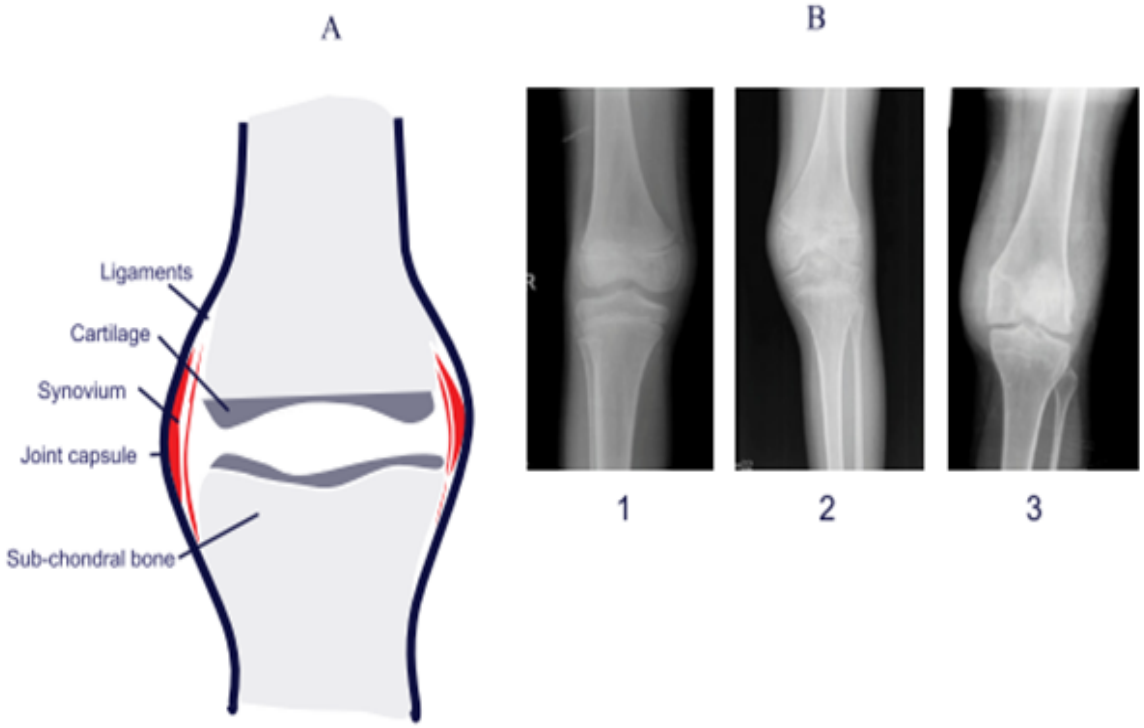

Figure 2. (A) The architecture of the joints includes synovial tissue, which allows for smooth movement by producing synovial fluid, which in turn nourishes and lubricates the articular cartilage. There is a synovial lining and a sublining in the synovial tissue.. (B) Panel 1 shows radiographs of normal knee joints; Panel 2 shows haemophilic patients with articular injury; and Panel 3 shows synovitis.

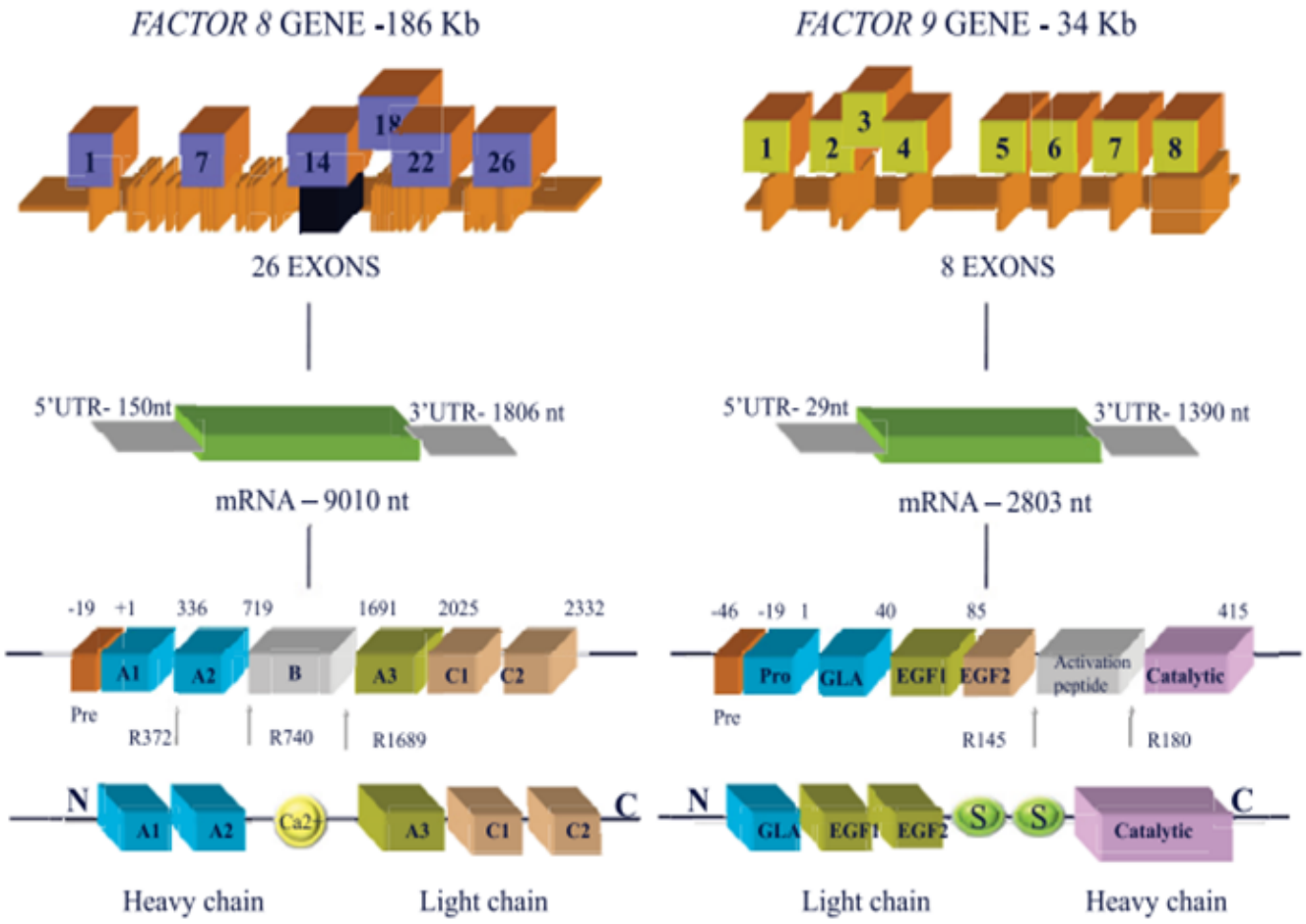

Figure 3. Proteins and genes involved in factors 8 and 9: The factor 8 gene encodes a messenger RNA of approximately 9 kilobase pairs and is 186 kilobases (kb) long. A precursor peptide of 2332 amino acids and an initial sequence of 19 amino acids make up the freshly produced factor VIII protein molecule. Factor VIII, when fully matured, has three copies of the A domain, two copies of the C domain, and one copy of the B domain. R372, R740, and R1689. These are the arginine residues that activate the proteolytic process. A metal ion bridge (Ca2+) connects the two heavy chains at the N and C ends of activated factor VIII, making the protein a heterotrimer.

Sickle Cell Disease

Hemoglobin is a protein present in the body which transports oxygen all over the body, sickle cell disease is the hereditary disorder in which defective hemoglobin occurs. This is a disagreeable and dangerous disease. One of the life threatening outcomes is acute chest syndrome that may develop when the red blood cells with a sickle-shaped structure are trapped within the blood vessels; the trap may result in pain crisis, or vaso-occlusive crisis. The second reason is stroke in which oxygen is not able to get to the brain. Although medications and chronic red blood cell transfusion may help to prevent these significant and even lethal outcomes, patients with sickle cell disease tend to be admitted to hospitals. Consider the case of sickle cell disease patients[22.23,24,25]. Their acute discomfort exceeds one a year and the average length of stay is five days in the hospital. Most of the patients visit the emergency department annually due to pain crisis purposes, and the patient visits the doctor 2-4 times

annually. It has been discovered that even at an early stage of research, a gene therapy can greatly decrease the number of painful vaso-occlusive crisis and acute chest syndrome in years after one treatment.

Beta Thalassemia

Beta thalassemia is a condition that is passed on to a number of the body organs and tissues and it interferes with the production of hemoglobin in the red blood cells. Crippling anemia and severe beta thalassemia patients might have an opportunity of a curative stem cell transplant. A very small proportion of patients who require a stem cell transplant actually receive one and even less are able to find donors who are a perfect match. The other option is to manage most of the severe cases whereby the patient is subjected to several transfusion sessions during his or her lifetime to keep his or her hemoglobin levels functional. In the US, a patient is expected to receive 17 transfusions each year, each having a time of several hours. The most significant possible negative outcomes of the said transfusions are iron overload. Excess of iron leads to heart related issues in most individuals diagnosed with severe type of beta thalassemia and the fact remains that most of those diseased people die before they attain the age of 30. It has been shown that a gene therapy which is at its advanced development stages can do away with regular blood transfusion as well as medications used to control side effects of treatment in the years after an initial dose of therapy in adults and children with beta thalassemia who are transfusion dependent.

Rarely Experienced Bleeding Disorders

Rare bleeding disorders (RBDs) Inheritance Rare bleeding disorders (RBDs), which contribute to 3-5 percent of all inherited deficiencies in coagulation factors, are typically transmitted autosomal recessively. Such deficits are fibrinogen, FII, (or prothrombin), FV, FV+, FVIII, FV7, FX, FXI, and FXIII. Until 1980, there was a paucity of information about RBDs, but there has been an explosion of published research about RBDs in the last decade, particularly about the molecular properties of RBDs. The rate of consanguinity is very high and this means high occurrence of RBDs that are also highly influenced by ethnic mix of the community. The symptoms of the RBDs may be very slight in nature, and very severe as well, and can vary dramatically among various illnesses and even among the same disorder. The paucity of knowledge about RBDs is largely because of the variability they present in the clinic that is associated with scarcity. The heterogeneous clinical feature, difficulties with identifying patients, constraints of laboratory tests, and unavailability of longitudinal clinical outcomes have all caused the complications in diagnosis, classification, and the need to treat these diseases. Efforts have been undertaken to pursue a unified approach to data collection to gain a better insight on their prevalence, their hemorrhagic manifestations and even to match clinical expressions of each of the factor deficiencies with its laboratory manifestation. The EN- RBD project proposes to accomplish just that by establishing a European network on rare bleeding disorders. The cross-sectional study that made it possible to analyze such a large amount of data on laboratory phenotype and clinical severity defined asymptomatic patients or grade I, II, or III based on location, prospective clinical impact, and bleeding trigger. Patients who had low coagulant activity showed a higher tendency to have spontaneous major bleeding and patients with sufficient FV+FVIII, FX, and FXIII deficiency were asymptomatic; this was observed most in fibrinogen deficiencies, combined FV+FVIII and FX, and FXIII deficiencies. In the case of FXI deficit, no linkage was proven whereas in the case of FV and FVII, there was a less powerful association. Such results did not only lead to the establishment of a new, practically useful system of classifications but also seemed to support the results of clinical experience and laboratory findings in individual patients[26,27]. The findings made in this research made it clear that the threshold within which the clinical symptoms are no longer observed is different in each RBD and this finding enhances the notion that these

bleeding diseases are unique and varied and that future studies must focus on each individual RBD. The Rare Bleeding Disorders Working Group is a branch of the Factor VIII & Factor IX Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), and analysis was carried out. The group took into account the EN-RBD findings and the findings of three other registries such as the UKHCDO, NARBD and the Indian registry, and also the data of the literature in English language.

The bleeding pattern of patients with RBDs is enormously different, but relative to hemophilia, the number of potentially fatal bleeding symptoms like CNS and musculoskeletal bleedings appears to be less. Most common symptoms are circumcision of the afflicted males and blood bleeding in the mucosal system following invasive surgery, birth and labor. Afibrinogenemia, FXIII and FX deficiencies are associated with excessive bleeding in the umbilical cord whereas CNS bleeding is prevalent in FXIII, fibrinogen, FVII and FX deficiencies. Gastrointestinal (GI) bleeding is less prevalent in all the RBDs with the possible exception of combination FV+FVIII deficiency, but is more frequent in FX insufficiency. The most common cause of hemorrhages are severe afibrinogenemia, FII, FX, FXIII deficits and the most common causes of soft tissue hematomas are fibrinogen, FII, and FX deficits. Besides the above mentioned symptoms of bleeding, the women also experience very heavy monthly bleeding that is linked to the menstrual cycles hence adding to their already challenging predicament. Menorrhagia, or the loss of blood over 80 mL with every menstrual cycle, and the complications that are related to it, such as chronic iron deficiency anemia, can be experienced by a woman with RBDs. Cases of bleeding during pregnancy have been reported among some women with afibrinogenemia and severe FX deficit and among women with afibrinogenemia with FXIII deficit recurrent miscarriages are occasionally witnessed[28]. Besides, when there is no replacement therapy within two or three days after birth, post-partum bleeding (PPH) will most probably occur. This may be inconveniencing to the women, on the whole, but to those who tend to experience coagulation, this is much more threatening to their livelihoods and their quality of life.

Diagnosis Genotype Analysis

The current approach to molecular diagnosis of the RBDs is based on the search of mutations in the genes of the coded coagulation factor. Rare varieties of this are a combined FV and FVIII coagulation deficiency due to mutations in the MCFD2 and LMAN1 genes, and a combined FX, FII, FVII, and FIX deficiency due to mutations in the GGCX and VKORC1 genes which are post-translational modification and vitamin K metabolism enzymes. Excluding a few cases of FXI, where it was shown that a dominant negative effect was exerted by a set of missense mutations resulting in heterodimerization between mutant and wild-type polypeptides, the inheritance pattern of all of the RBDs is autosomal recessive. 38 Information about previously known mutations that cause RBDs is readily available in the ISTH mutation database. Missense mutations are the most universally occurring gene abnormalities, making up half to three-quarters of known mutations, with the exception of LMAN1 variations, with 50 percent incidence of mutation being caused by insertions / deletions, and 9 percent incidence of mutation being caused by missense mutations. Although less than 15 percent of the gene variations in coagulation factors are inserted/ deleted mutations, it is 20-30 percent of the fibrinogen, FV, MCFD2, and FXIII variations. Of all the coagulation factors, the percentage contribution of splicing and nonsense mutations is 515% of all mutations, with a high rate of 20% in the LMAN1 gene. Changes in the 3' and 5' UTRs of the genes, at the fibrinogen, FVII, FXI and FXIII loci, are the most rare with a prevalence of less than 5 percent. In 5-10 percent of patients with severe deficiency of clotting factors, no genetic abnormality can be identified, despite remarkable advances in our understanding of the genetic nature of the RBDs. New directions in coagulation abnormalities among these patients could be unveiled by next generation sequencing

(NGS). Even though these genome-wide approaches are definitely promising, they are yet to be used in the research of RBDs where the underlying mutations are actually unidentified. Identified patients with RBDs can provide the base on which prenatal identification of RBDs in families can be developed when severe bleeding is recorded in a previous kid. Molecular characterisation and subsequent prenatal diagnosis that ensues are very crucial and helpful in areas of the globe that have scarce resources and high rates of consanguinity. Poor management of the RBDs implies that those patients in such locations have very minimal probability of surviving beyond childhood.

Genotype-Phenotype Correlation

Variation in the degree of bleeding is tremendous even within individuals of the same genotype and it is difficult to find genotype-phenotype associations in RBDs. Some of the observed variability may be attributed to modifier genes, which are located at genetic loci not equal to the main pathogenic locus yet the variability influences the illness phenotype. There is support in the literature that prothrombotic FV Leiden and prothrombin gene mutations are hereditary and that certain variants may exacerbate the symptom of bleeding and others moderate it.

Medical Care

On demand basis, the conventional approach to the treatment of RBDs comprises the use of the medication as soon as the bleeding starts. Replacement therapy is based on the use of cryoprecipitate, plasma-derived concentrates (PCC), fresh frozen plasma (FFP), or recombinant products. Besides that, non-transfusional types of adjuvant therapy like the use of antifibrinolytic amino acids may also be used alone or in combination with replacement therapy in case of the less severe cases of mucosal tract hemorrhage. In creating guidelines, one should remember that the lowest hemostatic level of the deficient factor, the topic of discussion pedagogically, its plasma half-life, which varies with age (as well as the people of the same age and level of factor deficiency), and even the nature of the bleeding episode affect the dosage and frequency of treatments. 2 Patients with RBDs did not achieve as much improvement in their quality of life as patients with hemophilia A and B did due to the improvement of the production of safe and effective medicines. The information on the site of the World Federation of Hemophilia (WFH) includes the information about all single units of product[29,30,31]. Cryoprecipitate and FFP have continued to uphold their role in the treatment of RBD in the world. PCCs may have FII, FVII, and FX in uncontrolled amounts as a general therapy against FII and FX deficits. Therefore patients, particularly under prophylaxis should be closely monitored to ensure that none of the factors does increase beyond 150 percent and hence increasing the risk of thrombosis. Currently, it is only a few countries in Europe that have legal permission to sell fibrinogen, FVII, FXI, and FXIII-specific concentrates that are made by plasma. Prophylaxis in patients with FX insufficiency has been possible due to the development of a freeze-dried human FX concentrate, which contains a portion of FIX. A new highly purified FX concentrate has just been a topic of a pharmacokinetics oriented clinical study. At present, there is no specific and appropriate treatment of FV and FV+FVIII patients. The only therapeutic option that is presently available is infusion of FFP. To hasten its commercialization, preclinical trials are in progress in anticipation of the application to the orphan drug designation by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). FV concentrate is relatively recently developed to be used by deficient patients. At present, there are two recombinant products in use to treat RBDs and one is rFVIIa, approved to treat FVII insufficiency but used off-label to treat FV and FXI deficit, and the other is rFXIII, and is a more recent product. The rFXIII has recently received approval to treat deficiency of FXIII-A in the US, Canada, EU and Australia. The latest UK guidelines on therapeutic products against coagulation disorders outline a considerable set of treatment options of RBDs such as dose, bleeding, surgery, pregnancy, and prophylaxis. Preventative treatment ought to be

considered where the cases are clinically severe [32,33]. The prophylaxis may be primary (i.e. initiated at a tender age in order to prevent bleeding) or secondary (i.e. given after bleeding to prevent re-bleeding or recurrences). Such factors in selecting a preventive treatment are the rate of bleeding, the risk of major spontaneous bleeding, and the possibility of long-term disability due to bleeding in a particular location despite on demand treatment including central nervous system, gastrointestinal, and joint bleedings. In all other cases except the extreme cases of FXIII deficiency and surgical operations there is no evidence to help to make recommendations regarding the use of the primary prophylaxis. Profibrinogenemia also requires some patients with afibrinogenemia that have a significant deficit of FV, FVII, and FX to take prophylaxis on a regular basis due to cerebral hemorrhage. In order to avoid cardiovascular and thromboembolic outcomes, patients who receive frequent and repeated replacement therapy should be monitored regularly. Unluckily, evidence regarding the proper management of such patients is not available.

Conclusion

Blood is a vital connective tissue that performs many essential activities, which are too many to count. Blood transfers oxygen, nutrition, hormones, and wastes all over the body with the help of plasma and the elements it consists of. Within the body, red blood cells serve the purpose of carrying oxygen to the body, white blood cells carry out the function of fighting against infections and diseases and platelets form clots and seal wounds of damaged tissues to different extents. The abundance of proteins and electrolytes among other chemicals in plasma is necessary in metabolic processes, immunological defenses, and homeostasis. Moreover, blood is vital to life since it adjusts the PH, maintains body temperature, and prevents disease and trauma. To maintain blood physiology constant with injuries and other physiological challenges on homeostasis, the complex pathways of clotting and buffering mechanisms are present. That is why, it is highly important to study about the types of blood disorders and abnormalities; timely detection and treatment of them can save people. The clinical and laboratory features of RBDs are rarely studied since they are not very common. Therefore, to enhance the amount of data that they gather and analysis strength based on this data, there is a necessity to establish global networks of treatment facilities. To determine a treatment plan that is acceptable and ensure that the hemostatic process is normal, one must establish the safe and minimal amount of coagulation factor to be present. At the same time, the clinical end outcomes that will be produced will facilitate setting up appropriate trials to observe the safety and efficacy of new drugs. In policy terms, the policies of orphan drug designation vary depending on the country, but act as a legislative incentive to the pharmaceutical companies to invest in research and development of innovative treatment solutions. An advantage in accessing a particular market, consultation with proficient people in the industry (in the form of protocol assistance or development consultation), assistance on behalf of regulators, and a quicker review are some illustrations of such incentives [34]. As much as this law has come a long way, the law may need some improvements. It would also be prudent to harmonise the various standards established by various regulatory institutions throughout the world. Consequently, new treatment options would be promoted, and the name and marketing authorization of orphan drugs would be simplified on the international level [35]. Above all, we should not ignore the introduction of a platform that would allow the stakeholders in the medical and scientific community, the pharmaceutical and health care institutions to engage in a candid dialogue on how the Orphan Medicinal Product Regulation has contributed to the growth of accessibility of novel orphan drugs to patients with the rare blood disorders.

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