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Specialty: Applied biochemistry

Topic

Cardiovascular diseases and blood groups, statistical frequency and relationship; A Retrospective study in Khenchela Province

Submitted by:

BOUZEKRI HAFSA

Members of the jury:

President:RAHAL Khaled	MA(A) University of Khenchela
Supervisor: BOUSSAA Abdelhalim	MA(A) University of Khenchela
Examiner:ZERAIB Azzedine	MC(B) University of Khenchela

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Dedication

To those who lit the torch of the Hirak

To its detained

To those who still believe in change

To Djamal ben Ismail, and everyone who resisted injustice until the light in their eyes dimmed

To every martyr

To Algeria…

I dedicate this humble work.

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Abstract

This study aims to investigate the relationship of blood group systems ABO & Rh (A+, A-, B+, B-, AB+, AB-, O+, O-) with cardiovascular disease, specifically: high blood pressure (HBP), Arrhythmia, Hyperlipidemia, Ischemic cardiomyopathy, Congenital cardiopathy, Myocardiopathy and Peripherical artery, n several regions in the wilaya of Khenchela. Using a statistical computer program; Statistica software, and analyzing the data obtained by Principal Compound Analysis (PCA).

Therefore, it was concluded that the blood group systems have a big linkage with cardiovascular diseases selected in this study, and that blood groups A+ and O+ are more susceptible to some diseases than other blood groups.

Keywords: Blood, group, disease, heart, cardiology.

الملخص

تهدف هذه الدراسة إلى معرفة مدى ترابط أنظمة الزمر الدموية ABO وريزوس (A +، A-، B +، B-، AB +، AB-، O +، O-) بأمراض القلب والأوعية الدموية ، وتحديداً: ارتفاع ضغط الدم (HBP) ، عدم انتظام نبضات القلب، فرط الدهون في الدم، اعتلال عضلة القلب الإقفاري، اعتلال القلب الخِلقي، اعتلال عضلة القلب والشريان المحيطي، وهذا في عدة مناطق بولاية خنشلة. استُخدم برنامج حاسوب إحصائي؛ برنامج Statistica، لتحليل البيانات التي تم الحصول عليها وذلك بواسطة "تحليل المركب الرئيسي" (PCA).

وعليه، تم الخلوص إلى نتيجة مفادها أن لأنظمة الزمر الدموية ارتباط وثيق بأمراض القلب والأوعية الدموية المدروسة في هذه المذكرة، وأن فصائل الدم +A و+O هما الأكثر عرضة لبعض الأمراض من غيرهما من بقية فصائل الدم الأخرى.

الكلمات المفتاحية: دم، زمرة، مرض، قلب، علم القلب.

Résumé

Cette étude vise à étudier la relation entre les systèmes de groupes sanguins ABO & Rh (A+, A-, B+, B-, AB+, AB-, O+, O-) avec les maladies cardiovasculaires, en particulier: l'Hypertension artérielle (HBP), l'Arythmie, l'Hyperlipidémie, l'Ischémie cardiomyopathie, Cardiopathie congénitale, Myocardiopathie et Artère périphérique, dans plusieurs régions de la wilaya de Khenchela. Utilisant un programme informatique statistique; logiciel Statistica, et en analysant les données obtenues par Composé principal analyse (CPA).

Par conséquent, il a été conclu que les systèmes de groupes sanguins ont un lien important avec les maladies cardiovasculaires sélectionnées dans cette étude, et que les groupes sanguins A+ et O+ sont plus sensibles à certaines maladies que d'autres groupes sanguins.

Mots clés: Sang, groupe, maladie, coeur, cardiologie.

General introduction

GENERAL INTRODUCTION

It is a fluid that transports oxygen and nutrients to the cells and carries away carbon dioxide and other waste products. Technically, blood is a transport liquid pumped by the heart to all parts of the body, after which it is returned to the heart to repeat the process. Blood is both a tissue and a fluid. It is a tissue because it is a collection of similar specialized cells that serve particular functions. These cells are suspended in a liquid matrix (plasma), which makes the blood a fluid. If blood flow ceases, death will occur within minutes because of the effects of an unfavourable environment on highly susceptible cells. This is the reason behind blood being one of the most important elements in the living body, and it has intrigued biologists since ancient times. Scientists researches began to dig into the secrets of this liquid by obtaining information about its nature, components, role, and types.

One of the most important components of blood is red blood cells or scientifically called erythrocytes, which carry on their membranes antigens that determine the type of blood carried by their owner, and this is what is called a blood group system such as the ABO blood system, which is the most common among humans. Blood types differ from one person to another according to their genetic information (genetic profile). Whereas the transmission of blood types is hereditary.

Over time, some scientific studies have shown that blood groups are not just distinctive symbols of blood, but actually, they have a relationship and a correlation between them and diseases.

This thesis is an attempt to reveal the association between ABO and Rh blood group systems and cardiovascular diseases using Statistica software, in which we use the Principal Component Analysis (PCA) on a data set belonging to a number of patients from different regions of the Wilaya of Khenchela.

This study mainly aims to:

- Analysis of the data set of the sample taken in the Wilaya of Khenchela regions with Statistica.
- Finding the correlation between blood types and cardiovascular diseases

In this thesis; the 2^{nd} and 3^{rd} chapters present the historical aspects and some background information on haematology and cardiopathy respectively, theories about correlation between ABO and Rh blood group systems and cardiovascular diseases are provided. Subsequent chapters present and discuss the statistical data that are found. This work is concluded with a recapitulation found in Conclusion section.

Before going to the heart of the matter, the reader, if he or she does not already have a knowledge of biology, must familiarize him or herself with a number of commonly used concepts and terminologies. The technical terminology and terms are easily understood. The reader may consult them at any time in the Glossary.

Theoretical part

Chapter 1: Glossary

Terminology

Chromosomes and Genes: In the human body, the nucleus of each body cell contains 46 small thread-like structures called chromosomes, arranged in 23 pairs. The length of each chromosome is divided to many small units called genes, which are important as they contain the different physical characteristics, which can be inherited including those of the blood groups.

Allomorphic genes (Alleles): Each gene has its own place called its locus along the length of the chromosome. However, a certain inherited characteristic can be represented by a group of genes, and the place or locus can be occupied by only one of these genes. Such genes are called alleles or allomorphic genes. For instance, every one belongs to one or other of the following blood groups: group A, group B, group O or group AB. Therefore, there are three allelomorphic genes which make up the ABO Blood group system such as gene A, gene B, and gene O. Only one of these alleles can occupy the special place or locus along the chromosomes for this blood group characteristic.

Body cells and mitosis: When body cells multiply, they do so by producing identical new cells with 46 chromosomes. This process is called mitosis.

Sex cells and meiosis: When sex cells are formed either male or female the pairs of chromosomes do not multiply but simply separate so that each of the new cells formed contains only 23 chromosomes not 46 as in the body cells. This process is called meiosis. However, during fortification when the egg and sperm unite, the fertilized ovum receives 23 chromosomes from each sex cell half of these from the male and half from the female and thus will contain 46 chromosomes which again arrange themselves in pairs in the nucleus. For example, a child who inherits gene A from its father and also gene A from its mother would be homozygous, where as a child who inherits gene A from its father and gene B from its mother would be heterozygous.

Dominant and recessive genes: A dominant gene will always show itself if it is present but a recessive gene will only show itself if there is no dominant one, that is if both genes are recessive. For example, in the ABO blood group system the gene A and B are dominant over gene O. Thus, if a child receives from its parents gene A and O it will belong to group A. In the same way if a child receives from its parents genes B and O it will belong to group B only if it receives gene O from both its parents will it belong to group O.

Genotype and phenotype: The genetic composition from a particular inherited characteristic is called the phenotype and the way this can be seen is called phenotype. Thus, if a person is group A (phenotype) his phenotype could be either AA or AO.

Chapter 2: Blood and blood group system

I. Blood

1. A brief history of haematology

"It's important to know whence we came, so that we may understand where we're going" —Todd Daniel, Ph.D.

Blood is an essential conduit for the immune system, hormonal messages, and fluid, and enables thermal homeostasis. The study of blood, or hematology _also spelled haematology_, is a broad and evolving field of medicine that has fascinated physicians and scientists throughout the ages. The history of haematology dates back to ancient Egypt and the use of blood-letting tools. A major breakthrough in the study of blood occurred in 1642 when Anthony van Leeuwenhoek built a microscope and identified blood cells. In 1770, William Hewson, the 'Father of Haematology', introduced the clotting features of blood and shared his knowledge of leukocytes, or white blood cells. It wasn't until 1818 that James Blundell successfully completed the first recorded blood transfusion between humans, but the world would have to wait almost another hundred years before Reuben Ottenberg used blood typing to conduct transfusions and identified the universality of type O blood.

Dutch microscopist Antonie van Leeuwenhoek's discovery of blood cells, in the 17th century (1674). As he, using a primitive, single-lens microscope, observed red blood cells (erythrocytes) and compared their size with that of a grain of sand, and English physiologist William Hewson's description of the different cell types, in the 18th century (1770), established the foundation on which the entire discipline of hematology, has been built. William Hewson amplified the description of red cells and demonstrated the role of fibrin in the clotting (coagulation) of blood. Rudolf Virchow (1821–1902), the 'Father of cellular pathology', was the first to recognize leukemia and to explain the mechanism of pulmonary thromboembolism. He documented that blood clots in the pulmonary artery can originate from venous thrombi, writing: "…the detachment of larger or smaller fragments from the end of the softening thrombus which are carried along by the current of blood and driven into remote vessels. This gives rise to the very frequent process upon which I have bestowed the name of Embolia."[1]

The subspecialty of haematology is said to have begun as a consequence of Max Wintrobe's characterization of normal blood values in the late 1920s. He refined the hematocrit as a quantitative measure of red cells and was the first to characterize anemias on the basis of their size; microcytic, normocytic, and macrocytic. The advent of better diagnostic techniques has improved our understanding of the pathophysiology related to blood and shapes the field today.

The discovery of the ABO blood group system in the first quarter of the 20th century made possible the transfusion of blood from one person to another without the serious ill effects that ensue when incompatible blood is given. The study of the blood disease anemia gained impetus

[1] Source: Thrombosis and Emboli, 1856

from the introduction of the hematocrit, an apparatus for determining the volume of red blood cells as compared with the volume of plasma, and the introduction in 1932 of a simple method of measuring the volume and hemoglobin (the substance that transports oxygen to the tissues) content of these cells. About 1920 the investigation of the role of food substances in the production of red blood cells led to discovery of the beneficial effects of liver extract in treating pernicious anemia and ultimately to the discovery of vitamin B12, the anti-anemic principle of liver. Parallel discoveries in nutrition, biochemistry, and the use of heavy and radioactive isotopes helped elucidate how hemoglobin is produced and aided in the recognition of changes that take place in disease.

After World War II the field of hematology broadened. Hematological studies of sickle cell anemia revealed that a variation in hemoglobin at the molecular level can be the underlying cause of disease. Simultaneous advances in techniques of protein and enzyme chemistry permitted recognition of a large number of other genetic disorders of hemoglobin synthesis (hemoglobinopathies).

The advent of molecular biology and molecular genetics has allowed researchers to study the mechanisms of diseases of platelet function, coagulation, and hematologic cancers such as leukemia and lymphoma.

Table 1: Timeline of major haematology landmarks

Year	Event
3255 BC	The oldest intact red blood cells ever discovered are found in Ötzi, a natural mummy of a man who died around that time.
460 BC – 377 BC	Greek physician Hippocrates teaches the humoral theory, a hypothetical system to explain illness in which balance equals health, and excess or deficiency equals illness.
1616	English physician William Harvey discovers **blood pathways**. Since then, many people try to use fluids such as beer, urine, milk, and non-human animal blood as blood substitute.
1642	Dutch scientist Antonie van Leeuwenhoek constructs a **microscope** and distinguishes **blood cells**.
1667	French physician Jean-Baptiste Denys and Richard Lower separately report giving the **first human blood transfusion**. Within 10 years, transfusing the blood of animals to humans becomes prohibited

	by law, delaying transfusion advances for about 150 years.
1821 – 1902	German physician Rudolf Virchow disproves a prominent view that phlebitis (inflammation of a vein) causes most diseases. Virchow demonstrates that masses in the blood vessels result from "**thrombosis**" (his term) and that portions of a thrombus could become detached to form an "embolus" (also his term).
1901	Austrian biologist Karl Landsteiner and his associates discover the **ABO blood group system**, and define the different blood groups: A, B, AB, and O. Such names refer to the different kinds of antigens on the surface of the red blood cell.
1932	A simple method of measuring the volume and **haemoglobin** is introduced.
1937	Karl Landsteiner and Alexander S. Wiener identify the **Rh factor** (an abbreviation of "Rhesus factor") in blood. The Rhesus-system is the second most important blood group system after ABO.
1961	Till and McCulloch published the first of their breakthrough series of experiments confirming that **haematopoiesis occurs in the bone** marrow and indicating that haematopoiesis could be studied as a quantitative science.
1968	Rh immune globulin (RhIg) is first licensed as a human plasma-derived product consisting of **IgG antibodies** to the **D antigen**. It is used to prevent immunization to the D antigen in D-negative individuals and for the treatment of immune thrombocytopenia (ITP).
1980	Molecular biology is applied to the study of blood groups.

2. Blood

Blood is a very unique fluid composed of many cellular elements as well as a liquid portion consisting of proteins, amino acids, carbohydrates, lipids, and other macromolecules and low-molecular-weight precursors. Organs of the body affected by, or used to, transport blood include the blood vessels, bone marrow, lymph nodes, and spleen. Proteins in the body are also involved in bleeding and clotting.

The hematopoietic system is characterized by high cell turnover and replenishment throughout one's life. The pluripotent hematopoietic stem cell (HSC) is the progenitor for all

cells that arise in blood. The cellular elements that arise from this stem cell include red blood cells, white blood cells, and platelets. Normal white blood cells in the peripheral circulation include neutrophils, monocytes, eosinophils, basophils, and lymphocytes. Since the HSC also gives rise to cells of the lymphoid system, the study of hematology also includes the lymph nodes and lymphoid tissue. There is no specific organ for hematologic disorders, and its diseases arise within the bone marrow, the lymph nodes, or the intravascular compartment. The latter includes the endothelial cells lining blood vessels and the proteins in the blood plasma. The circulating cell-endothelial cell interface and the rheologic aspects of blood coursing through the intravascular compartment also influence haematology and its many parts.

Whole blood consists of red and white blood cells, as well as platelets suspended in a liquid referred to as blood plasma. According to the American Red Cross, plasma is 92% water and makes up 55% of blood volume. The permeability of blood plasma is equal to 1.

Red blood cells make up slightly lower blood volume than blood plasma; about 45% of whole blood. As you probably already know, these types of blood cells contain hemoglobin, which in turn consists of iron that helps transport oxygen throughout the body. The permeability of red blood cells is slightly less than 1, (1 – 3.9e-6). Or to put it in words, red blood cell particles are diamagnetic.

Due to their magnetic properties, red blood cells may be separated from the plasma via a magnetophoretic approach. If the blood were to be in a channel subject to a magnetophoretic force, we could control where the red blood cells and the plasma go within the channels. In other words, because the red blood cells have different permeability, they can be separated from the flow channel. However, such methodology is beyond the year 1980.

2.1. The composition of blood

As mentioned before, blood contains different types of cells, such as red blood cells (RBCs), white blood cells (WBCs), platelets, and the liquid called plasma.

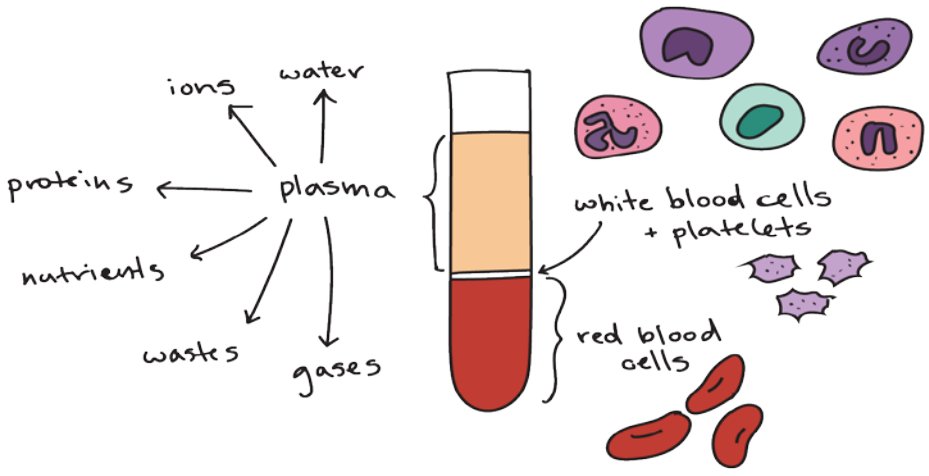

Figure 1: Blood components

If a test tube of blood is left to stand for half an hour, the blood separates into three layers as the denser components sink to the bottom of the tube and fluid remains at the top. The straw-colored fluid that forms the top layer is called plasma and forms about 60% of blood. The middle white layer is composed of white blood cells and platelets, and the bottom red layer is the red blood cells. These bottom two layers of cells form about 40% of the blood. (Figure 1)

Plasma is mainly water, but it also contains many important substances such as proteins (albumin, clotting factors, antibodies, enzymes, and hormones), sugars (glucose), and fat particles. All of the cells found in the blood come from bone marrow. They begin their life as stem cells, and they mature into three main types of cells: red blood cells, white blood cells, and platelets. In turn, there are three types of white blood cells: lymphocytes, monocytes, and granulocytes, and three main types of granulocytes: neutrophils, eosinophils, and basophils.

A sample of blood can be further separated into its individual components by spinning the sample in a centrifuge. The force of the spinning causes denser elements to sink, and further processing enables the isolation of a particular protein or the isolation of a particular type of blood cell. With the use of this method, antibodies and clotting factors can be harvested from the plasma to treat immune deficiencies and bleeding disorders, respectively. Likewise, red blood cells can be harvested for blood transfusion.

2.2. Haematopoiesis

Hematopoiesis – the formation of blood cellular components – sometimes spelled haematopoiesis [*haima*, blood. *poiēsis*, to produce something]. Haematopoiesis occurs during embryonic development and throughout adulthood to produce and replenish the blood system. Studying haematopoiesis can help scientists and clinicians to understand better the processes behind blood disorders and cancers. Furthermore, haematopoietic stem cells (HSCs) can be used as a model system for understanding tissue stem cells and their role in ageing and oncogenesis. In this part, I provide an overview of the process of haematopoiesis, highlighting the sites of hematopoiesis in human organism, the involved factors in the emergence of HSC and the importance of cell formation and self-renewal.

In humans, haematopoiesis begins in the yolk sac and transitions into the liver temporarily before finally establishing definitive haematopoiesis in the bone marrow and thymus. Experiments with human embryos confirm observations in the haemangioblast, a common precursor for endothelial and haematopoietic cells.

HSCs in the BM self-renew throughout adult life in order to continuously produce downstream progeny and by definition they are multipotent; they have the capacity to generate all blood lineages. Serving as the “roots” of the hematopoietic “tree”, HSCs hold tremendous proliferative potential: the transfer of single HSCs into irradiated hosts can generate detectable progeny in all blood lineages. HSCs produce terminally differentiated blood cells through a step-wise process of differentiation and proliferation. These steps are considered to be irreversible,

such that once a given lineage potential is lost, it cannot be regained by normal physiological mechanisms. There are many signals, both intracellular and extracellular, that govern the process of hematopoietic differentiation. Cytokines, for example, have the capacity to direct lineage specification during at least some stages of hematopoietic differentiation.

The most common sites of EMH (Extra-Medullary Haematopoiesis) are the liver and spleen, but other, rarely reported sites include lymph nodes, paraspinal region, mediastinum, breast, central nervous system, peripheral nerves, orbit, pancreas, oropharynx, lungs, pericardium, heart, gastrointestinal tract, thyroid gland, kidney, adrenal gland, and almost every organ.

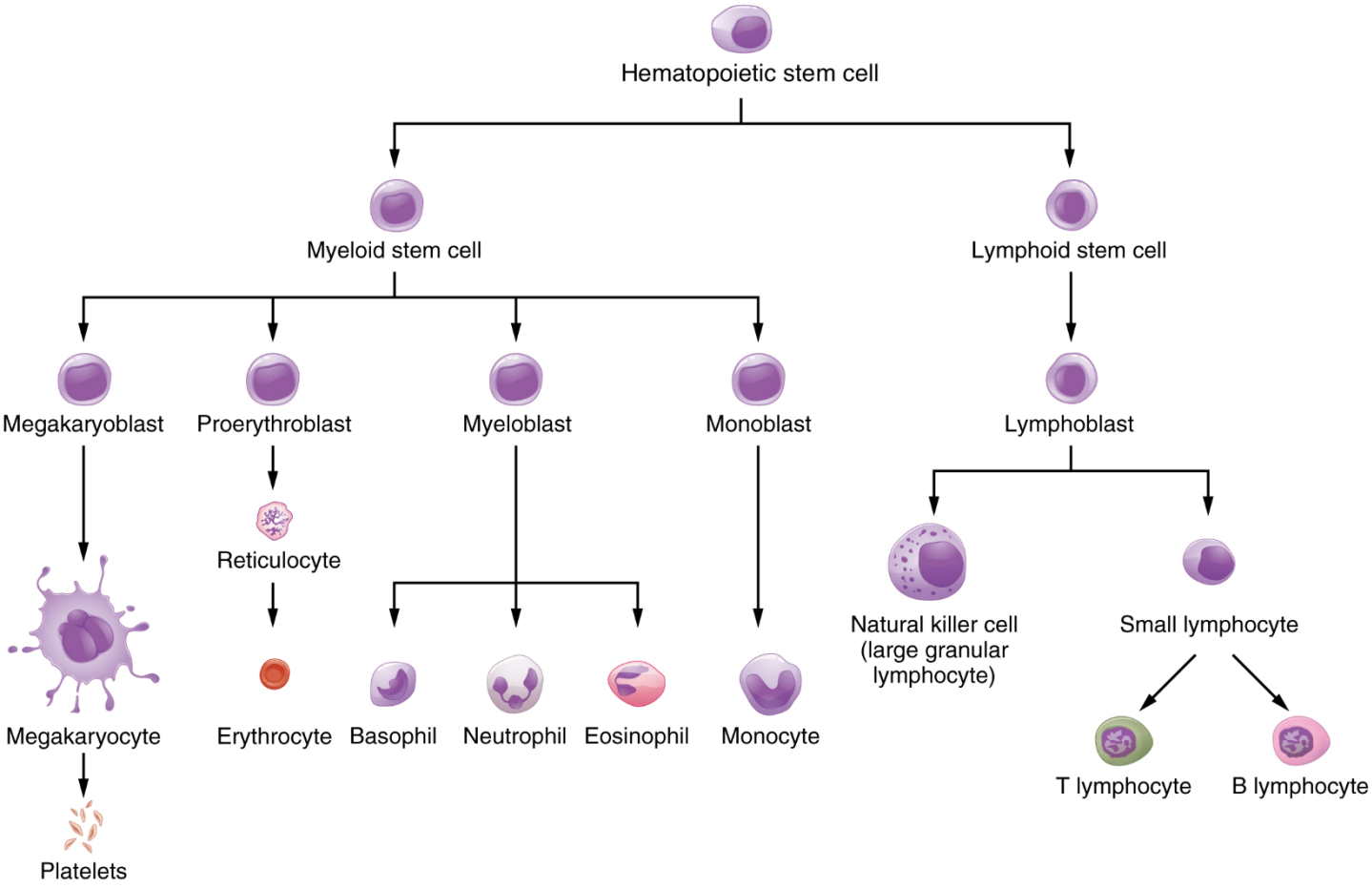

Figure 2: General overview of haematopoiesis (the haematopoiesis tree)

2.2.1. Haematopoisis stages

2.2.1.1. Primitive stage

Blood development in vertebrates involves two waves of haematopoiesis: the primitive wave and the definitive wave. The primitive wave, which involves an erythroid progenitor, gives rise to erythrocytes and macrophages during early embryonic development. The primary purpose of the primitive wave is to produce red blood cells that can facilitate tissue oxygenation as the embryo undergoes rapid growth. In mammals and avians, these erythroid progenitor cells first appear in blood islands in the extra-embryonic yolk sac early in development. The primitive wave is transitory, however, and these erythroid progenitors are not pluripotent and do not have renewal capability.

a. Anatomy of yolk sac

The yolk sac is a small, membranous structure situated outside of the embryo with a variety of functions during embryonic development. It attaches ventrally to the developing embryo via the yolk stalk. The yolk stalk is a term that may be used interchangeably with the vitelline duct or omphalomesenteric duct.

It serves to connect the yolk sac to the midgut, which is an early derivative of the gastrointestinal system. The yolk sac has several critical biological functions, including primitive hematopoiesis and germ cell production.

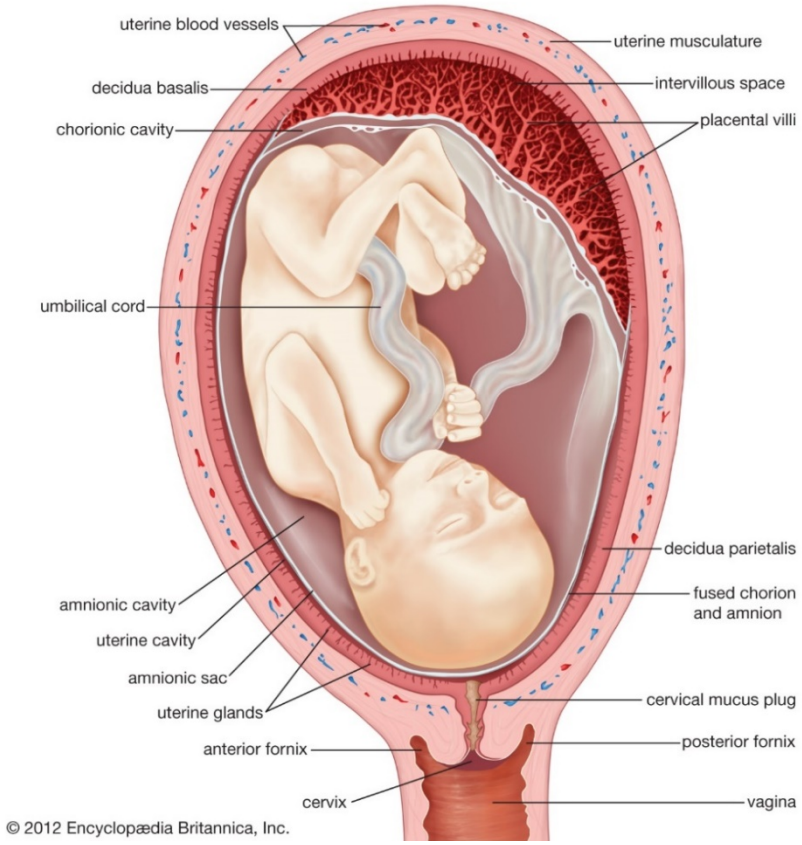

Figure 3: Anatomy of uterus during pregnancy

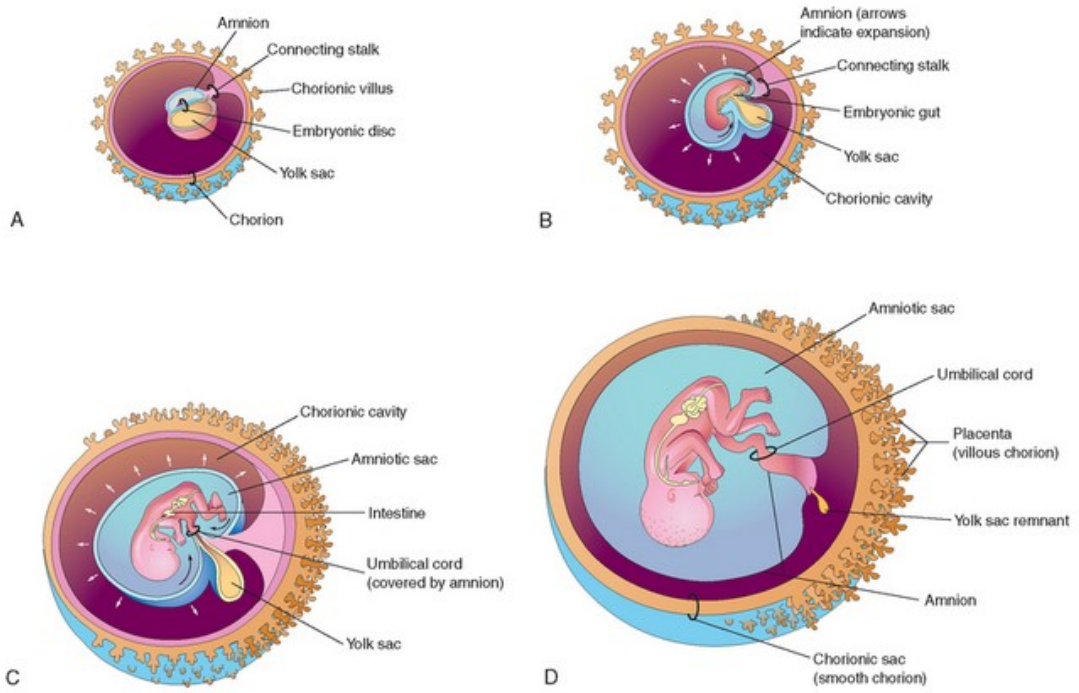

Figure 4: Evolution of the yolk sac with the embryo

b. The yolk sac haematopoiesis

As we already said, during fetal development, haematopoiesis occurs in multiple waves throughout the developing embryo and fetus, including extraembryonic YS[2], the para-aortic region of the embryo, fetal liver, and placenta before eventually homing to the bone marrow where it occurs just before birth. The first haematopoiesis is observed in the yolk sac (often referred to as primitive haematopoiesis) producing embryonic type erythroblasts that have large nuclei and express embryonic globin genes, and primitive type macrophages.

The following wave is consisting of yolk sac and embryo-derived adult type haematopoiesis that produces EMPs[3] and lymphoid precursors. Finally, the first BM[4]-repopulating haemato-poietic stem cells are produced in the AGM[5] region. These haemato-poietic stem cells seed the fetal liver and the placenta and expand to support haematopoiesis after birth. In the meantime, YS-derived EMPs are considered to seed the liver as well to support haematopoietic homeostasis during embryo development. The fetal liver is the major haematopoietic organ during development, supporting active erythro-myeloid haematopoiesis and haemato-poietic stem cells expansion. In this sense, the fetal liver niche marks a unique site for understanding the cell cycle

[2] Yolk sac
[3] erythro-myeloid progenitors
[4] Bone marrow
[5] aorta-gonad-mesonephros

dynamics of developing haemato-poietic stem cells in contrast to the quiescent state of adult bone marrow haemato-poietic stem cells.

The first blood precursors generated at this stage of development give rise to primitive erythroid precursors, erythroid cells with unique characteristics, only found during early embryogenesis and which role is to rapidly deliver oxygen to the fast-expanding embryo. Macrophage and megakaryocyte progenitors are also generated during this earliest wave of blood emergence. The next wave of blood specification starts later with the emergence of erythro-myeloid progenitors (EMPs) within the yolk sac. These EMPs produces definitive erythrocytes and most myeloid lineages. B and T lymphoid progenitors are generated in the yolk sac and in the intra-embryonic para-aortic splanchnopleura region. All types of fetal and adult T cells are produced by these early progenitors, including αβ and γ δ subsets. In the case of B lymphocytes, the potential of this first wave of progenitors is restricted to the production of innate-type B1 and marginal zone B cells subsets. Recent studies have also established that tissue resident macrophages of the brain, lung and liver are generated during these earliest waves of hematopoietic development.

2.2.1.2. Definitive stage

As the embryo continues to develop, the haematopoiesis process moves to the liver, the spleen, and bone marrow, and begins producing other types of blood cells, we call this definitive haematopoiesis, which by contrast, occurs later in development, notably at different time points in different species. In most organisms, there is a transient wave of definitive haematopoiesis that occurs in the blood islands and produces progenitors called erythroid-myeloid progenitors (EMPs). Definitive haematopoiesis later involves HSCs, which are multipotent and can give rise to all blood lineages of the adult organism. In vertebrates, definitive HSCs are born in the aorta-gonad-mesonephros (AGM) region of the developing embryo. They migrate to the fetal liver and then to the bone marrow, which is the location for HSCs in adults.

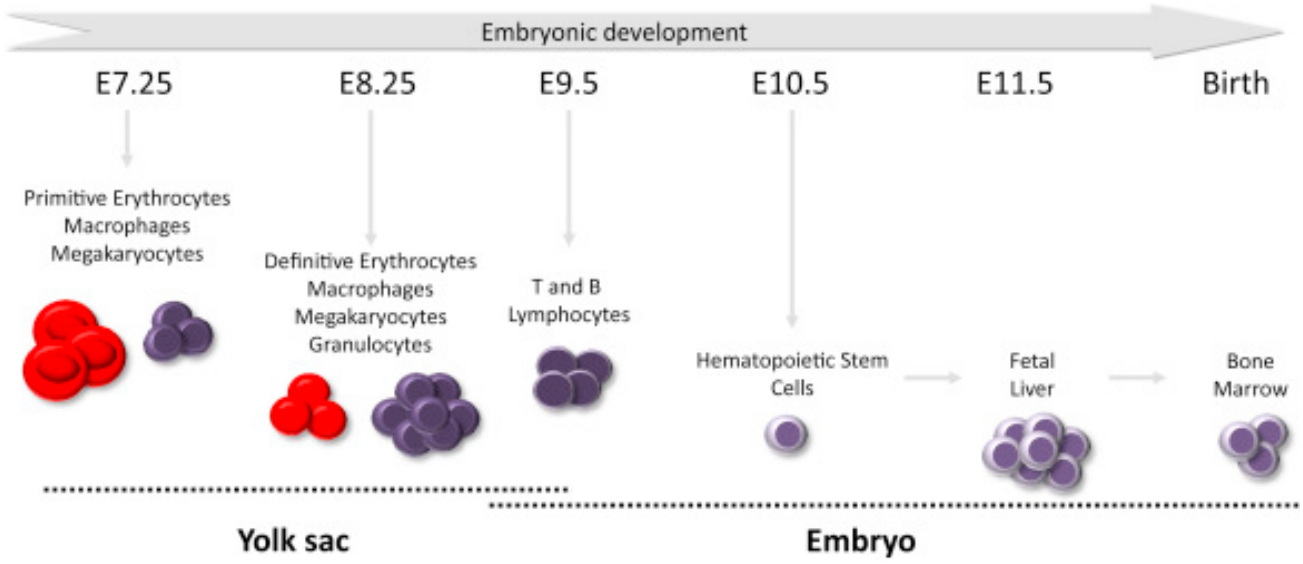

Figure 5: Embryonic haematopoiesis development

2.2.1.2.1. Bone marrow

a. Anatomy of bone marrow

Bone marrow is the soft, spongy, gelatinous tissue found in the hollow spaces in the interior of bones. The average weight of this tissue is about 4% of the total body weight. Progenitor cell (stem cell) lines in the bone marrow produce new blood cells and stromal cells. Bone marrow is also an important part of the lymphatic system.

Bone marrow consists of stem cells, which are large, primitive, undifferentiated cells supported by fibrous tissue called stroma. The bone marrow consists of two types of cellular tissue; red bone marrow, known as myeloid tissue, and yellow bone marrow, known as fatty tissue. Both types of bone marrow are enriched with blood vessels and capillaries.

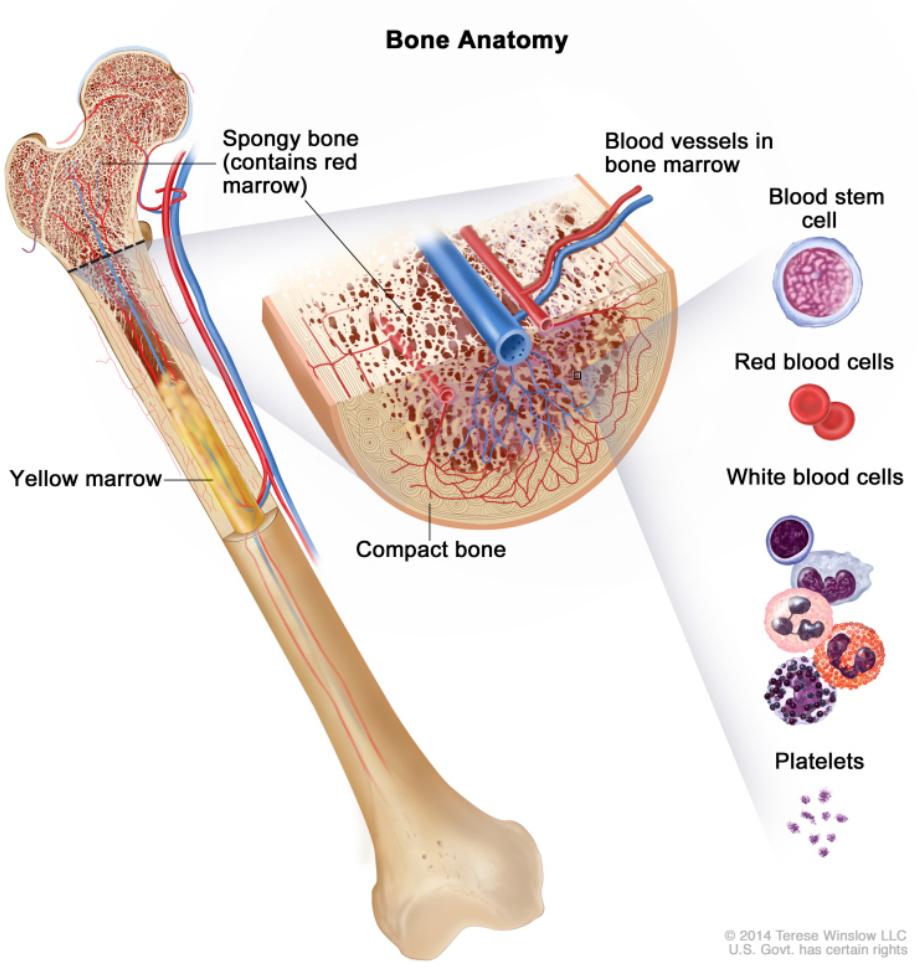

Figure 6: Anatomy of normal bone

b. Bone marrow haematopoiesis

The bone marrow, in adult life, is the only source of both red cells and the granulocytes. Bone marrow is a rich mixture of developing and mature blood cells, as well as fat cells and other types. Arteries pierce the outer walls of the bones, enter the marrow, and divide into fine branches, which ultimately coalesce into large venous sacs (sinusoids) through which blood flows sluggishly. In the surrounding hematopoietic tissue, newly formed blood cells enter the general circulation by penetrating the walls of the sinusoid. In the adult the bone marrow produces all of the red cells. The lymphatic tissues, particularly the thymus, the spleen, and the lymph nodes, produce the lymphocytes. The reticuloendothelial tissues of the spleen, liver, lymph nodes, and other organs produce the monocytes. The platelets are formed from bits of the cytoplasm of the giant cells (megakaryocytes) of the bone marrow.

Both the red and white cells arise through a series of complex transformations from primitive stem cells, which have the ability to form any of the precursors of a blood cell. Precursor cells are stem cells that have developed to the stage where they are committed to forming a particular type of new blood cell. By dividing and differentiating, precursor cells give rise to the four major blood cell lineages: red cells, phagocytic cells, megakaryocytes, and lymphocytes. The cells of the marrow are under complex controls that regulate their formation and adjust their production to the changing demands of the body. When marrow stem cells are cultured outside the body, they form tiny clusters of cells (colonies), which correspond to red cells, phagocytic cells, and megakaryocytes. The formation of these individual colonies depends on hormonal sugar-containing proteins (glycoproteins), referred to collectively as colony-stimulating factors (CSFs). These factors are produced throughout the body. Even in minute amounts, CSFs can stimulate the division and differentiation of precursor cells into mature blood cells and thus exert powerful regulatory influences over the production of blood cells. A master colony-stimulating factor (multi-CSF), also called interleukin-3, stimulates the most ancestral hematopoietic stem cell.

Bone cavities are predominantly filled with active hematopoietic red bone marrow, the volume of which gradually decreases with age and is subsequently replaced with fat (yellow bone marrow) which gradually fills the entire marrow cavity through dynamic and reversible processes.

The bone marrow hematopoietic microenvironment, which is also known as the bone marrow hematopoietic niche, consists of marrow stroma cells, the cytokines they secrete, microvessels, and nerves. It was found that the bone marrow hematopoietic niche had two distinct states: the homeostatic niche and the reconstituting niche, but the precise definition of these niches remains to be determined. The HSC niche is also divided into the endosteal niche and sinusoidal niche. Endosteal niche is localized at the inner surface of the bone cavity, wherein the HSCs are in contact with osteoblasts and might serve as a reservoir for long-term HSCs storage in the quiescent state. The sinusoidal niche, on the other hand, consists of sinusoidal endothelial cell lining blood vessels, which provide an environment for short-term HSCs proliferation and

differentiation. Both niches act together to maintain hematopoietic homeostasis. Hematopoietic stem/progenitor cells further differentiate into two major categories of myeloid progenitor cells and lymphoid progenitor cells.

Myeloid progenitor cells have the potential to differentiate into myeloid lineage, while lymphoid progenitor cells have the potential to differentiate into lymphoid sub-lines (figure 8).

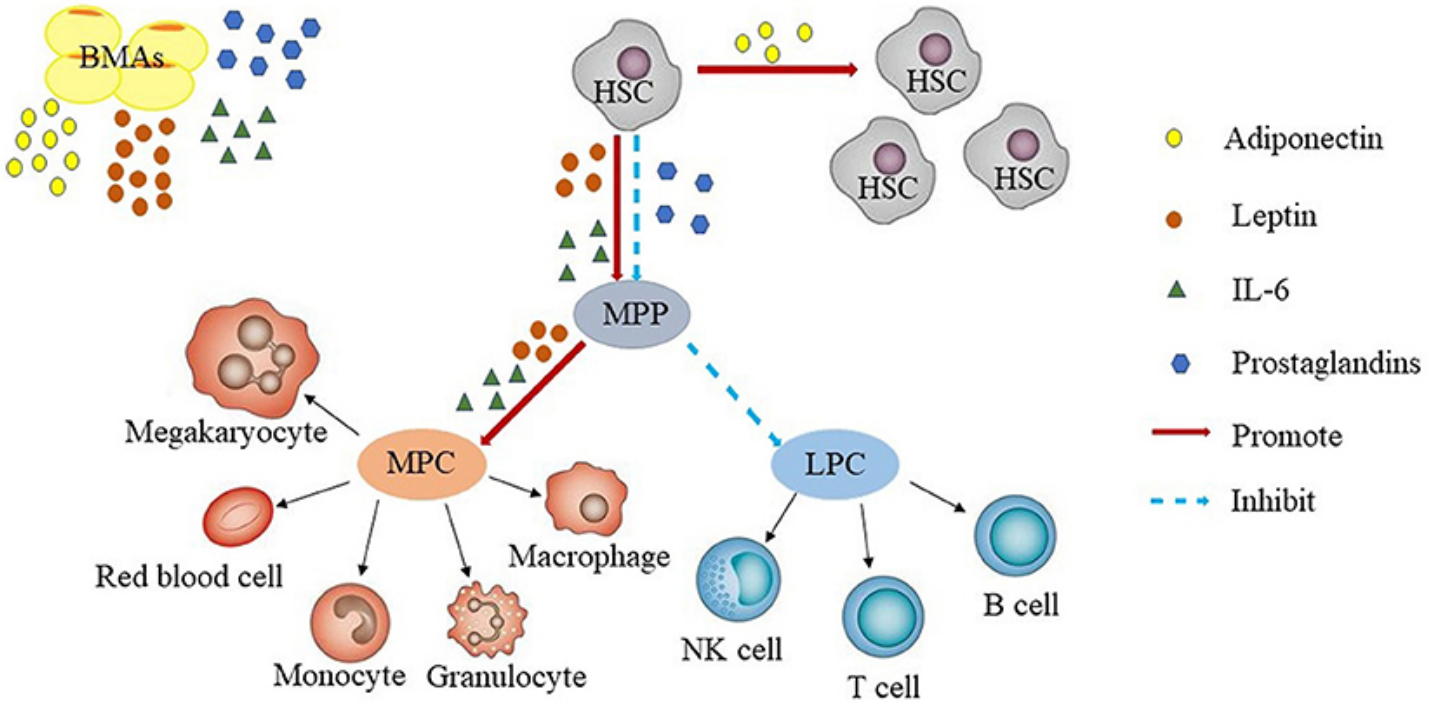

Figure 7: Bone marrow adipocytes and haematopoiesis

2.2.1.2.2. Liver

a. Anatomy of liver

The liver is located in the upper right-hand portion of the abdominal cavity. It is a reddish-brown, lobed mass that weighs about 3 to 3.5 pounds and sits just under the diaphragm and on top of the stomach, right kidney, and intestines. The liver contains millions of cells called hepatocytes. The liver holds about (13%) of the body's blood supply at any given moment. The liver consists of 2 main lobes. Both are made up of 8 segments that consist of a thousand lobules (small lobes). These lobules are connected to small ducts (tubes) that connect with larger ducts to form the common hepatic duct.

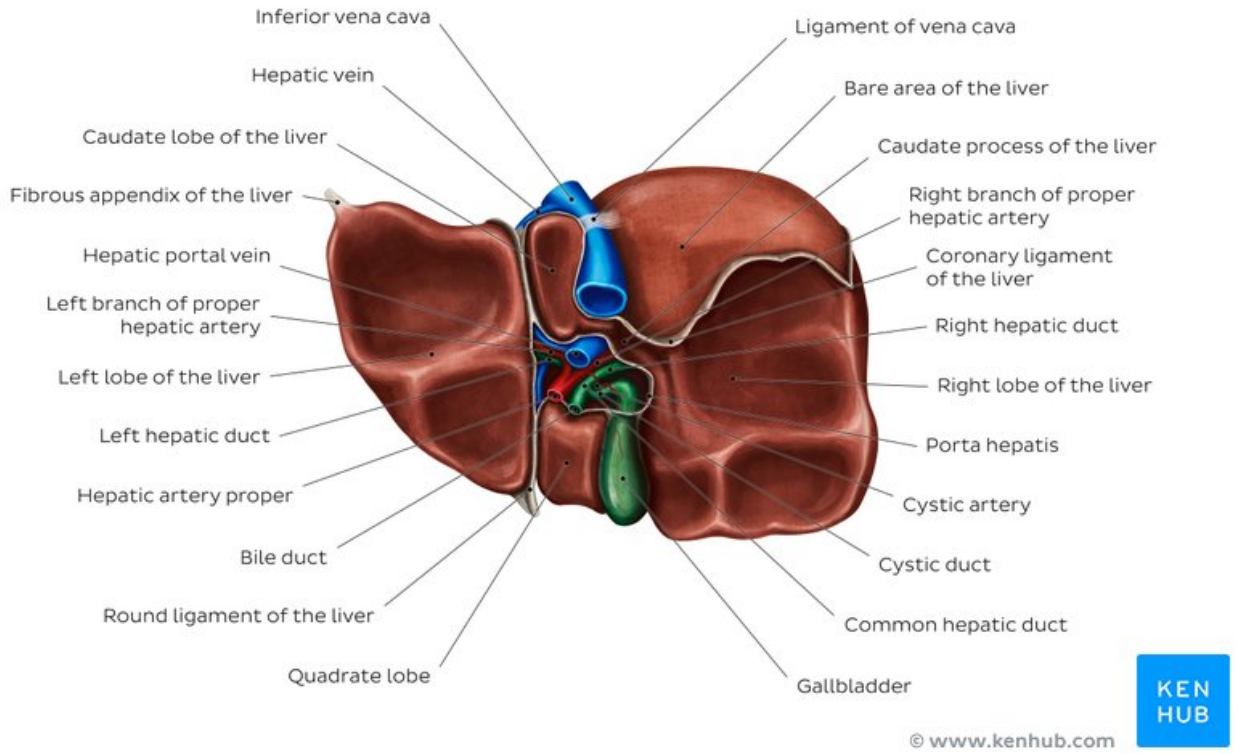

Figure 8: Anatomy of normal liver

b. Hepatic haematopoiesis

Hematopoiesis is the main function of the liver during prenatal development. As the hepatoblasts begin expanding in the primitive liver bud, the organ acquires the function of haematopoiesis. Hematopoiesis requires a specific microenvironment that produces signals to attract hematopoietic cells and regulates their proliferation and differentiation. A complex of cell types including hepatoblasts creates the hematopoietic microenvironment of the fetal liver. Recently, hepatoblasts have been shown to play an important role in the regulation of erythropoiesis; they produce erythropoietic cytokines such as stem cell factor and erythropoietin, which are responsible for increasing the numbers of erythroid progenitors. However, the exact mechanism of the cessation of hematopoiesis during later stages of liver development remains unknown.

On the other hand, hematopoietic cells also positively regulate hepatic morphogenesis. Studies show that hematopoietic cells produce OSM[6] that stimulates the functional maturation of

[6] Oncostatin M

hepatocytes through gp130[7], an OSM receptor subunit. Gp130 knockout livers display defects in maturation of hepatocytes. Thus, hematopoiesis and hepatopoiesis are truly a symbiotic relationship during development.

The figure below describes cell types and molecular cross talk. HSC receive IGF2, TPO, and angptl2 and 3 from hepatocytes and SCF from endothelial cells. At the same time, macrophages produce OSM to promote maturation of hepatocytes.

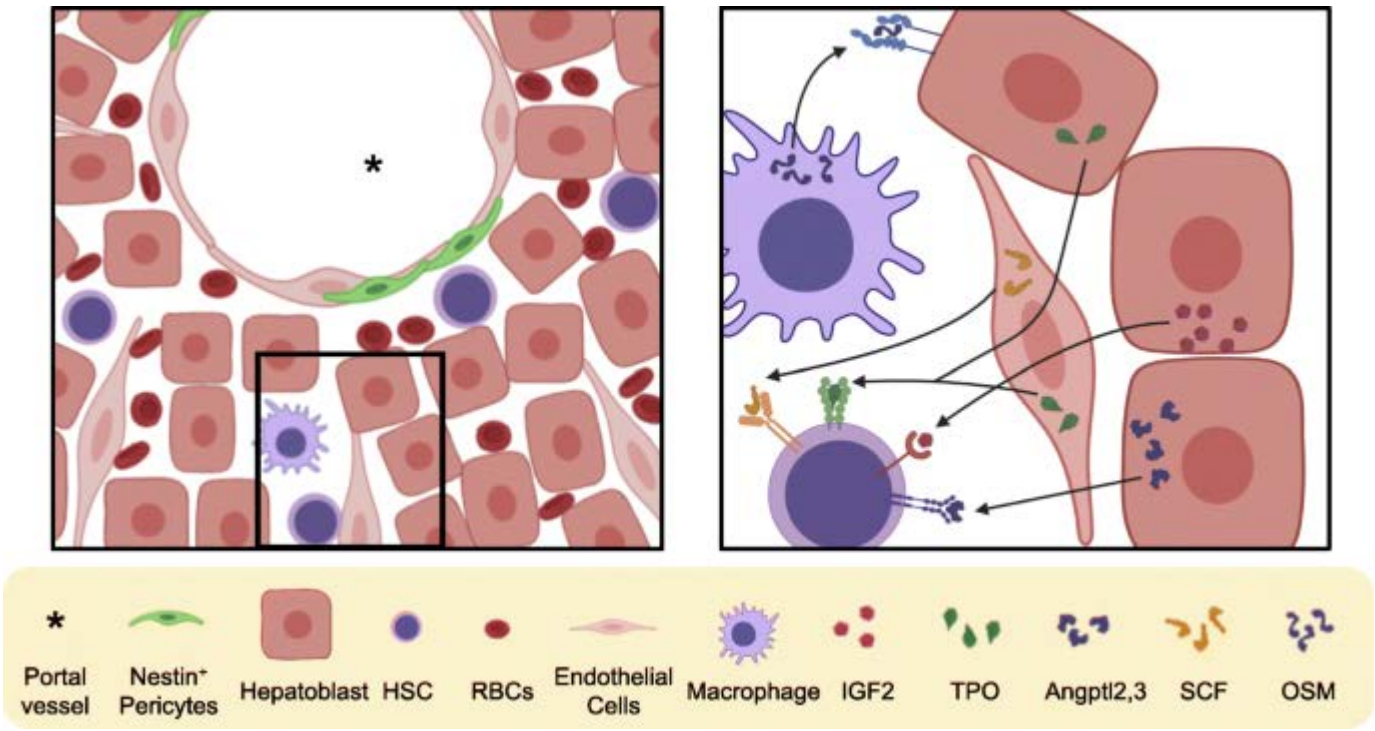

Figure 9: HSC niche in fetal liver

2.2.1.2.3. Spleen

a. Anatomy of spleen

The spleen is located in the upper left quadrant of the abdomen, under cover of the diaphragm and the ribcage, and therefore cannot normally be palpated on clinical examination (except when enlarged). It is an intraperitoneal organ, entirely surrounded by peritoneum (except at the splenic hilum). The spleen is connected to the stomach and kidney by parts of the greater omentum – a double fold of peritoneum that originates from the stomach.

The spleen has a slightly oval shape. It is covered by a weak capsule that protects the organ whilst allowing it to expand in size. The outer surface of the spleen can be anatomically divided into two: Diaphragmatic surface which is in contact with diaphragm and ribcage, and a visceral

[7] Glycoprotein 130

surface that is in contact with the other abdominal viscera. It has anterior, superior, posteromedial and inferior borders. The posteromedial and inferior borders are smooth, whilst the anterior and superior borders contain notches.

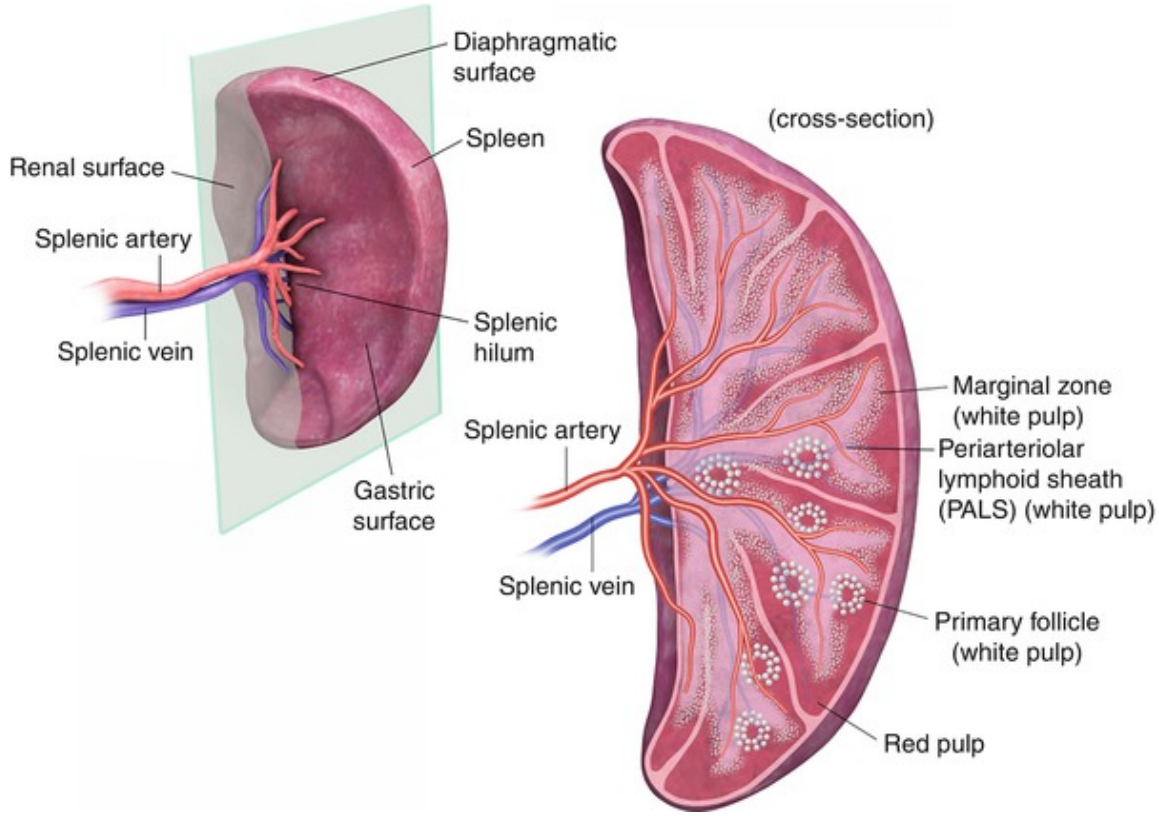

Figure 10: Normal splenic anatomy

b. Splenic haematopoiesis

It has long been assumed that spleen fills the role of an emergency or backup site for cell development at times of stress or disease. Indeed, the importance of bone marrow over spleen in hematopoiesis is evident since neonatally splenectomised live being can maintain normal bone marrow hematopoiesis. However, a distinct role for spleen in hematopoiesis has not yet been fully investigated in terms of development of individual cell subsets. Hematopoiesis in the embryo and fetus can be detected in the spleen during the third month of gestation. As the marrow becomes the predominant site of the blood production between the sixth and seventh fetal month, the splenic role in hematopoiesis wanes quickly. During embryogenesis, spleen harbors myeloid cells seeding from fetal liver and does not appear to become colonized with HSC until around the time of birth. Evidence that splenectomy in newborn mice results in a dramatic increase in colony forming cells in liver suggests that HSC entering spleen at this time may seed directly into spleen from fetal liver rather than from bone marrow. Spleen could therefore become colonized by HSC during development resulting in an endogenous HSC

population. Such a model would not however preclude later or additional entry of bone-marrow-derived HSC at times of stress or inflammation, or following stem cell transplantation.

In older children and adults hematopoiesis is limited to the bone marrow, but the spleen can revert to its embryologic role when marrow function is compromised such as in the myeloproliferative disorders, lymphomas and leukemias. Without functional marrow, hematopoiesis occurs in the liver and spleen, and these organs become the major source of blood production.

In uterus, the spleen is partially responsible for hemoglobin synthesis from the 10th through the 25th week of pregnancy. After birth, the primary function of the spleen shifts to the following major roles: Filtration, iron metabolism, prevention of infection, red blood cell and platelet storage.

2.2.1.2.4. Thymus

a. Anatomy of thymus

The thymus gets its name from its silhouette. It is shaped much like a thyme leaf, a common cooking herb. It has two separate lobes divided by a central medulla and a peripheral cortex and is formed with lymphocytes and reticular cells. The reticular cells form a mesh that is filled with lymphocytes. It is located just below the breast bone. It is relatively large in infants and grows until puberty. In adulthood, it starts to slowly shrink and become replaced by fat. It can weigh only 5 grams in elderly adults.

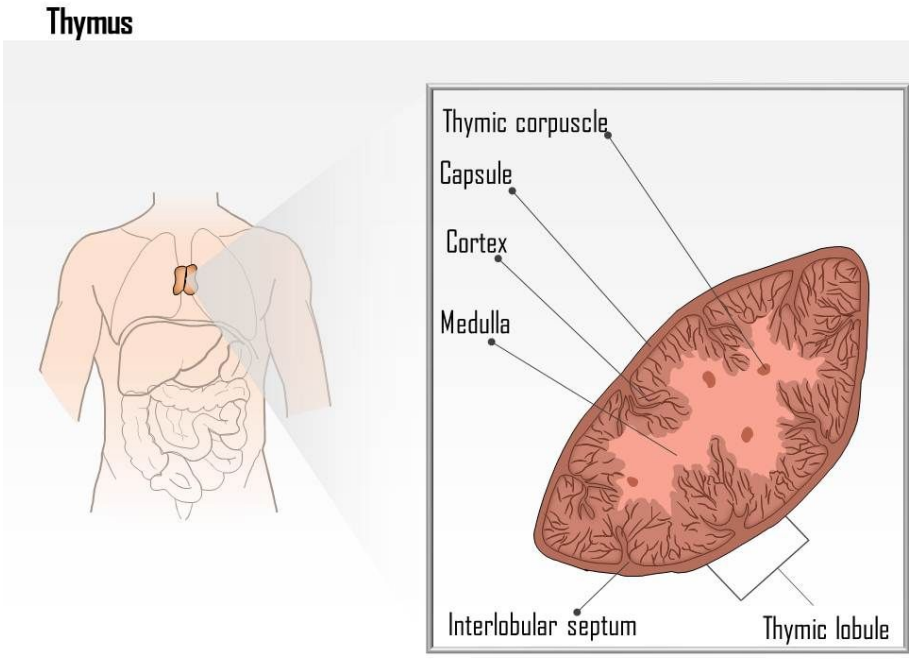

Figure 11: Anatomy of normal thymus

The thymus consists of two lobes, merged in the middle, surrounded by a capsule that extends with blood vessels into the interior. The lobes consist of an outer cortex rich with cells and an inner less dense medulla. The lobes are divided into smaller lobules 0.5-2mm diameter, between which extrude radiating insertions from the capsule along septa. The cortex is mainly made up of thymocytes and epithelial cells. The thymocytes, immature T cells, are supported by a network of the finely-branched epithelial reticular cells, which is continuous with a similar network in the medulla. This network forms an adventitia to the blood vessels, which enter the cortex via septa near the junction with the medulla. Other cells are also present in the thymus, including macrophages, dendritic cells, and a small amount of B cells, neutrophils and eosinophils.

In the medulla, the network of epithelial cells is coarser than in the cortex, and the lymphoid cells are relatively fewer in number.

b. Thymus haematopoiesis

While most hematopoietic lineages develop in the bone marrow (BM), T cells uniquely complete their development in the specialized environment of the thymus. And while T cells complete the majority of their development in the thymus, they ultimately originate from hematopoietic stem cells (HSCs) residing in the bone marrow (BM). Derived from these stem cells are various downstream progenitors that first lose the capacity for self-renewal (a defining feature of HSCs) and then progressively become more restricted in their lineage potential. Through a process that remains largely undefined, rare numbers of these progenitors mobilize out of the BM into the circulation, where they gain access to the thymus. These circulating progenitors will then migrate across the thymic endothelium to enter the organ itself. Following thymic entry, the cells will continue to differentiate while proliferating dramatically. Over the course of several weeks, these progenitors will proceed down the well-described intrathymic development stages. Cells begin the process lacking expression of both CD4 and CD8 co-receptors, then undergo a developmental checkpoint that leads to the co-expression of both CD4 and CD8 on so-called CD4+CD8+ double-positive (DP) cells. Following a second checkpoint, they downregulate one of the co-receptors to become either a CD8+ or CD4+ single-positive thymocyte. These cells will subsequently migrate from the thymus to take up residence in the periphery as naïve T cells.

While these major landmarks in this long process are known, many of the mechanistic details remain unclear

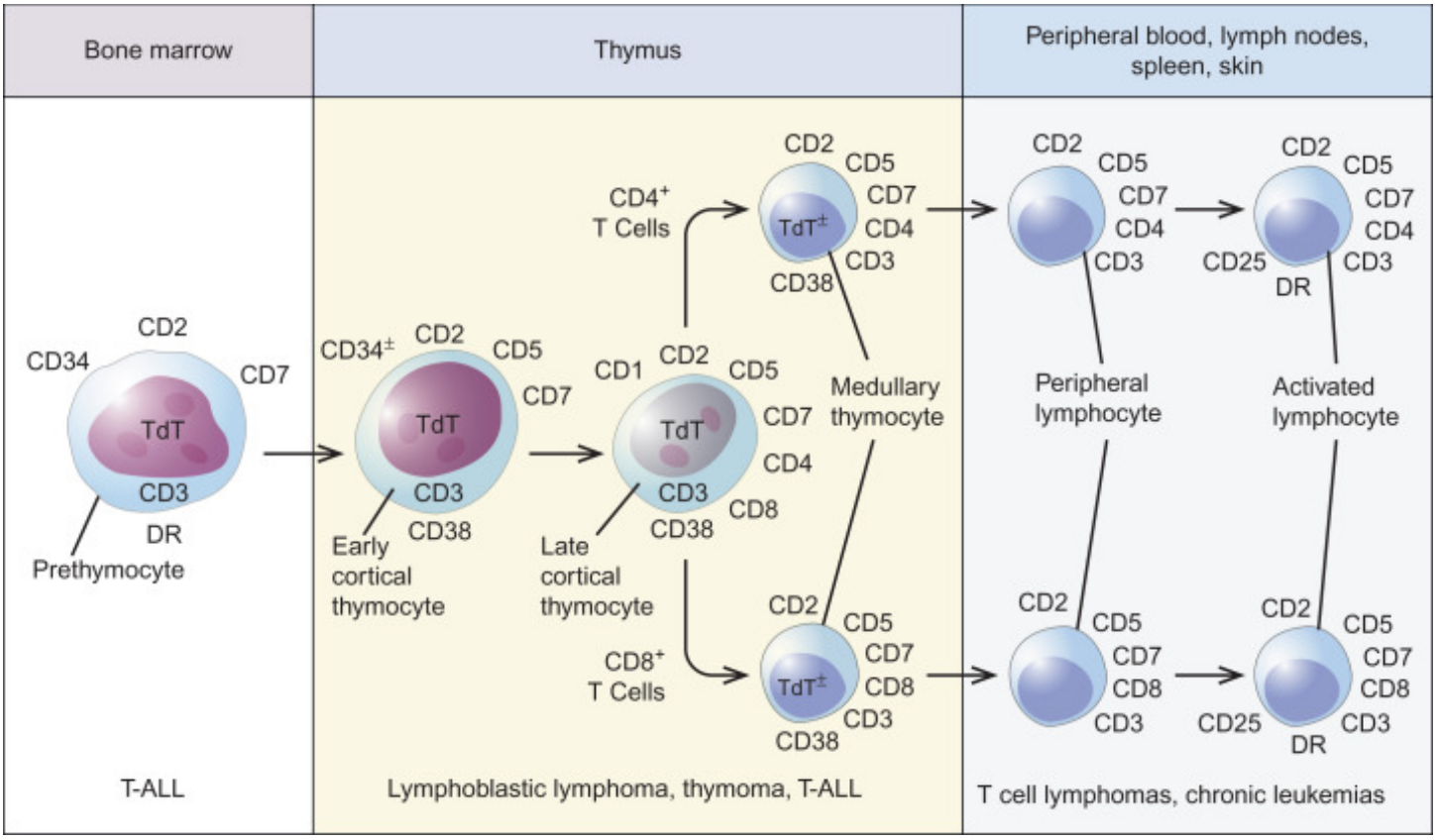

Figure 12: The maturation of the T cell from the bone marrow to the thymus to the peripheral blood, lymph nodes, spleen, and skin

2.2.1.2.5. Lymph nodes

a. Anatomy of lymph nodes

Lymph nodes are kidney-shaped and receive lymph via multiple afferent vessels, and filtered lymph then leaves via one or two efferent vessels. Nodes typically have an associated artery and vein, which terminates into a high endothelial venule (HEV). The HEV is the site of trans-endothelial migration of circulating lymphocytes due to T and B-cell endothelial surface receptors. Lymph nodes usually range in size from 1 to 2 cm and are enclosed in an adipose tissue capsule. Normal size depends upon location, as well as the axis which is being measured. The long axis should be 1 cm or less. They are considered pathological if they lose their oval shape, if there is a loss of the hilar fat, if there is an asymmetrical thickening of the cortex and if they are persistently enlarged.

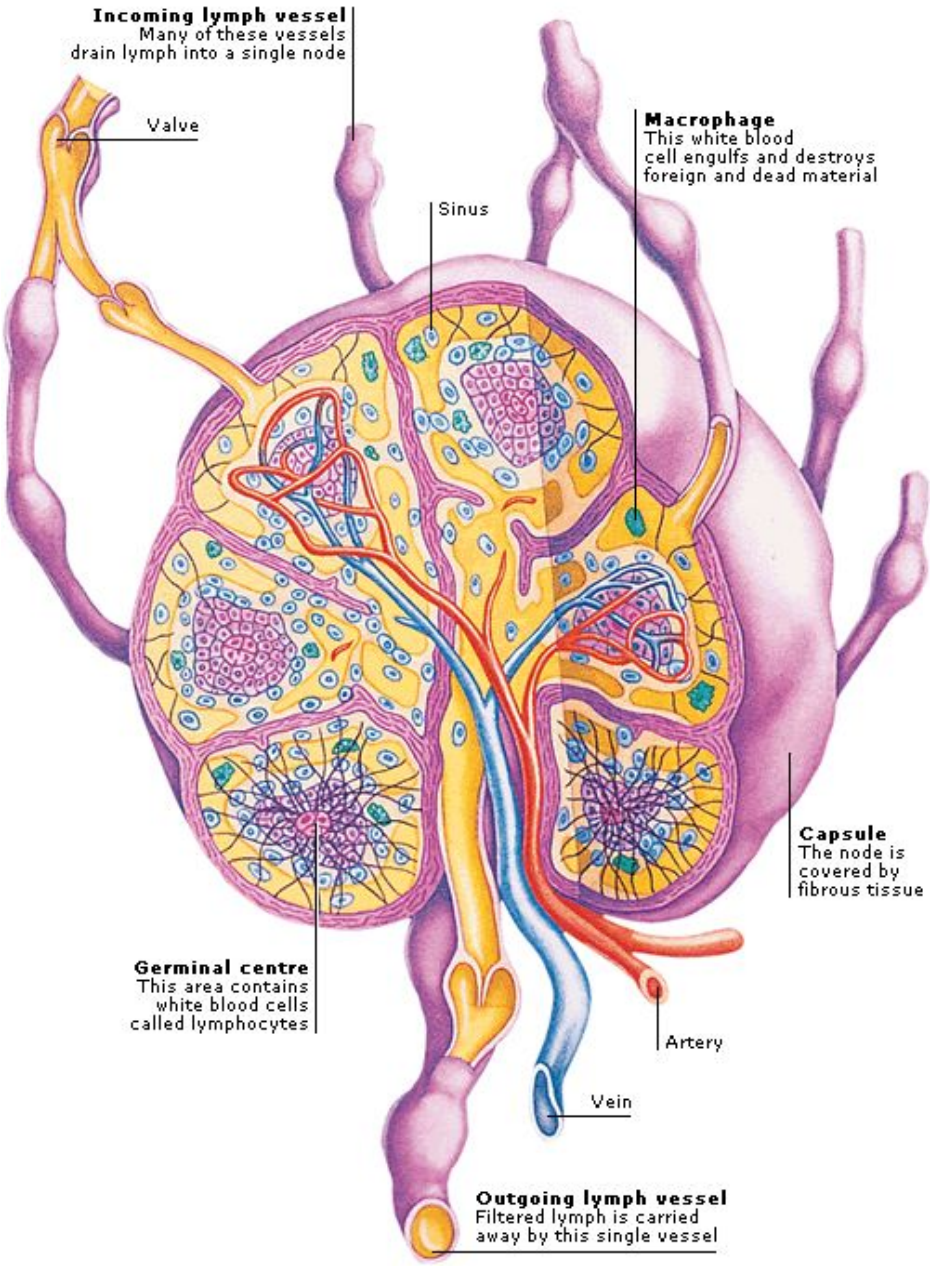

Figure 13: Anatomy of normal lymph nodes

a. Lymph nodes haematopoiesis

Lymph nodes may be a site of extramedullary hematopoiesis (EMH). EMH in lymph nodes typically occurs as a physiologic response to a dramatic loss or increased need for additional blood cells.

Examples of inciting factors include hemorrhage, infection, severe inflammation, myelofibrosis, and neoplasia. EMH is characterized by a mixture, to varying degrees, of myeloid, erythroid, and megakaryocytic cells and is primarily present within the lymph node medullary

cords. One lineage of hematopoietic cell may predominate, and various degrees of immaturity may be seen. EMH should be distinguished from inflammatory infiltrates and granulocytic leukemia. Inflammatory infiltrates in the lymph node are generally mature in development and may be a single or mixed cell type. Granulocytic leukemia is characterized by high numbers of immature neoplastic myeloid cells that involve multiple organs. Previous terms for extramedullary hematopoiesis include "hematopoietic cell proliferation" and "myeloid hyperplasia."

2.2.2. The involved factors in the emergence of haematopoiesis

Many factors and signaling pathways regulate the emergence of HSCs. Factors secreted from the endoderm as well as those produced by the somitic mesoderm, which help specify the dorsal aspect of the aorta, play an important role. The transcription factor COUPTF-II[8] and CDX-HOX[9], along with Notch1 are involved in induction of the AGM[10]. Studies using human embryonic stem cells have shown that factors like Hedgehog (Hh) and bone morphogenetic protein (BMP) promote blood production *in vitro*.

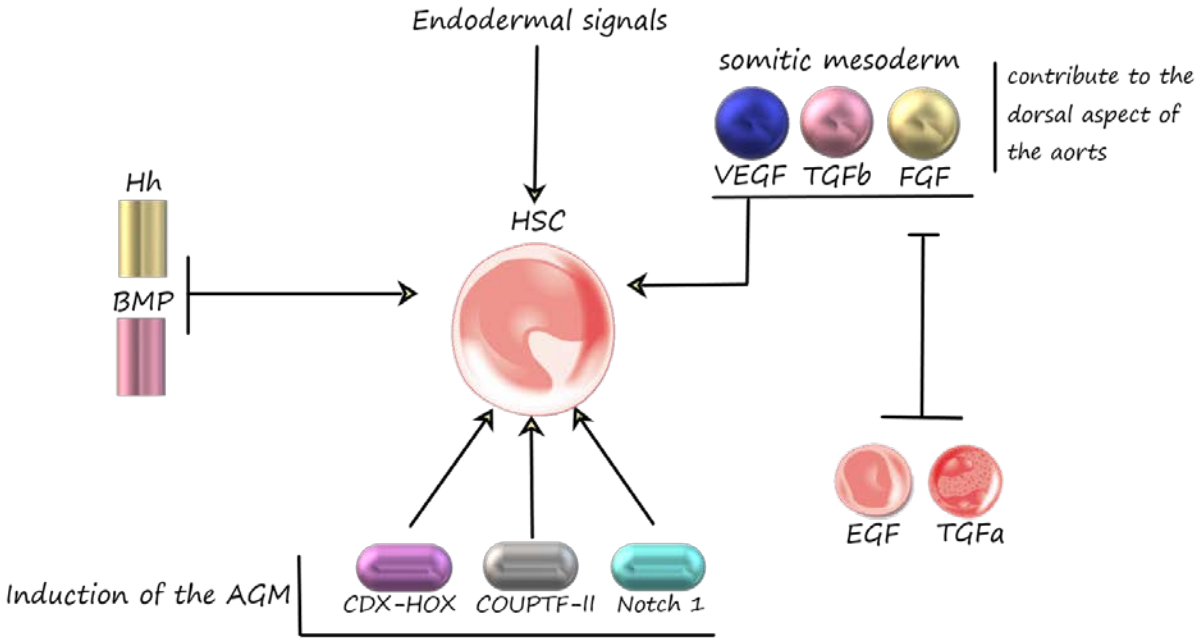

Figure 14: Factors involved in the emergence of haematopoiesis

[8] Chicken ovalbumin upstream promoter transcription factor 2
[9] Caudal homebox-posterior hox genes
[10] Aorta-gonad-mesenephros

2.2.3. The medical significance of haematopoiesis

Haematopoiesis is regulated to ensure an adequate supply of blood cells. The pluripotent haematopoietic stem cell differentiates via committed haematopoietic progenitors dependent upon bone marrow stroma, specific growth factors, and genetic programming.

The haematopoietic stem cell has the capability of self-renewal and significant plasticity. The consequences of bone marrow failure leading to pancytopenia include anemia, infection propensity and bleeding.

2.3. Erythrocytes (the red blood cell)

2.3.1. Erythrocyte structure and composition

Every second, two to three million erythrocytes are produced in the bone marrow and released into the circulation. Also known as erythrocytes, RBCs[11] are the most common type of cell found in the blood, with each cubic millimeter of blood containing four to six million cells. With a diameter of only 6 µm, RBCs are biconcave in shape; this shape increases their surface area for the diffusion of oxygen across their surfaces. In non-mammalian vertebrates such as birds and fish, mature RBCs do have a nucleus. Erythrocytes are small enough to squeeze through the smallest blood vessels, which makes them exposed to high pressure, and this is the main reason why their life period is shorter than the other types of cells, they circulate around the body for up to 120 days, at which point the old or damaged erythrocytes are removed from the circulation by specialized cells (macrophages) in the spleen and liver.

Erythrocytes are composed mainly of haemoglobin (35%), in addition to water (60%), lipids (5%), such as lecithin, cephalin and cholesterol, proteins (glutathione), lipoproteins (elenin), enzymes (glycolytic system), glucose, amino acids, ions (Cl, PO4, HCO3) and non-protein nitrogenous substances, for instance, urea, NH4, creatin and uric acid.

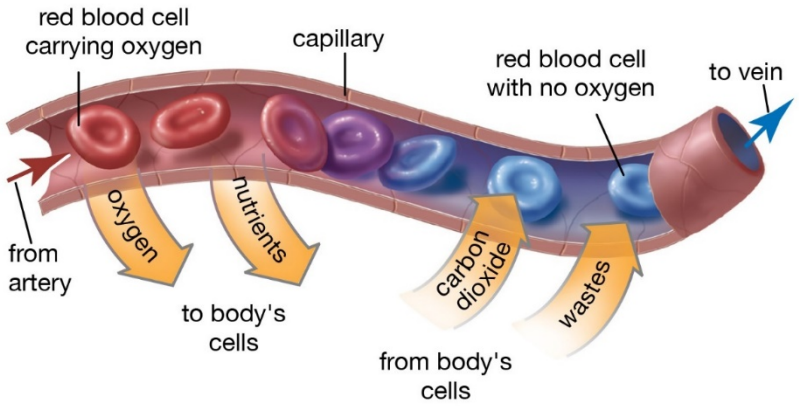

Figure 15: Erythrocytes; from artery to vein

[11] Red Blood Cell

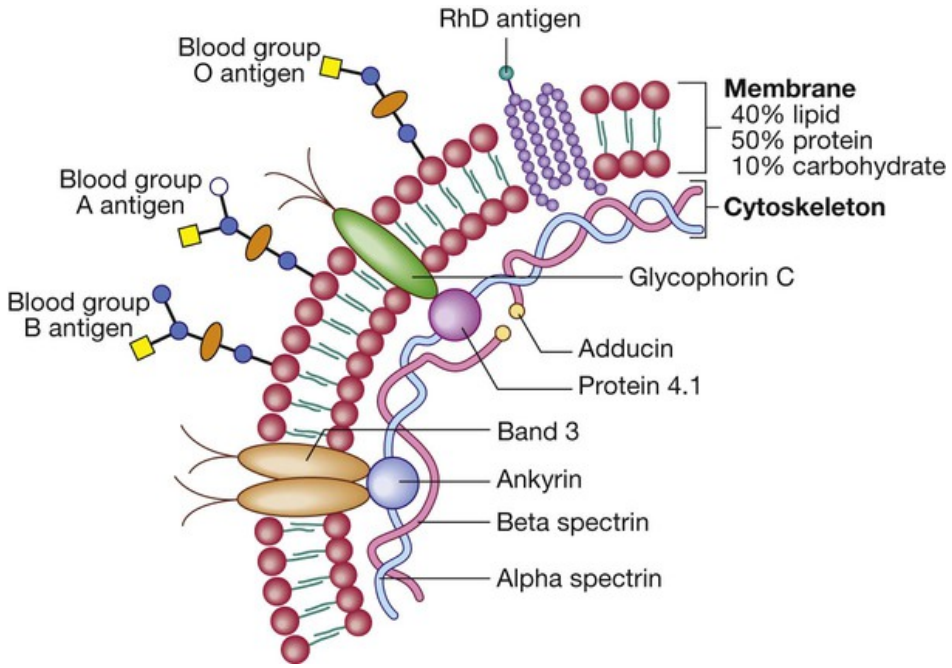

Figure 16: Normal erythrocyte cytoskeleton

2.3.1.1. Haemoglobin

In humans, as in all mammals, the mature RBC is anucleate. This allows the cell more room to store haemoglobin. Haemoglobin [Gk. hem, *blood*, and L. *glob*, ball] contains four globin protein chains, each associated with heme, an iron-containing group. Iron combines loosely with oxygen, and this way oxygen is carried in the blood. If there is an insufficient number of red blood cells or if the cells do not have enough haemoglobin, the individual suffers from anemia and has a tired-down feeling.

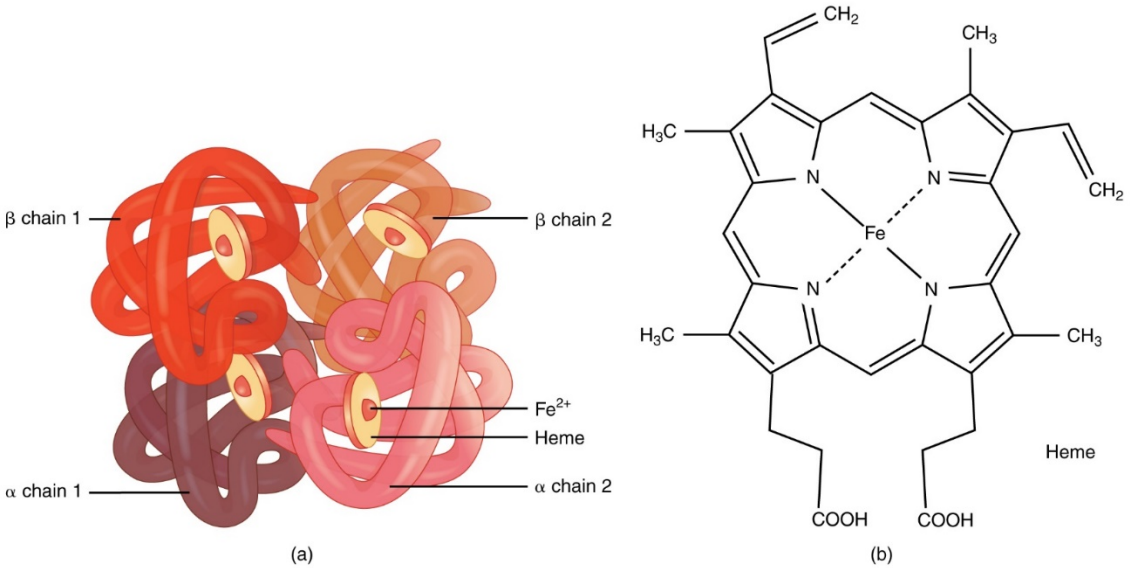

Figure 17: Haemoglobin structure

2.3.2. Erythropoiesis

Red blood cells are manufactured continuously in the red bone marrow of the skull, the ribs, the vertebrae, and the ends of the long bones. The growth factor erythropoietin, which is produced when an enzyme from the kidneys acts on a precursor made by the liver, simulates the production of red blood cells. Now available as a drug, erythropoietin is helpful to persons with anemia and is also sometimes abused by athletes who want to increase performance

Before they are released from the bone marrow into blood, red blood cells lose their nucleus and synthesize haemoglobin. So, we can divide erythropoiesis (the formation of red blood cells) to three phases; **Ribosome synthesis** when it is an early erythroblast, **Haemoglobin accumulation** when it is a late erythroblast, and the last phase is the **ejection of nucleus** to transform from a normoblast to an anucleate erythrocyte. After living about 120 days, they are destroyed chiefly in the liver and the spleen, where they are engulfed by large phagocytic cells. When red blood cells are destroyed, haemoglobin is released. The iron is recovered and is returned to the red bone marrow for reuse. The heme portions of the molecules undergo chemical degradation and are excreted by the liver as bile pigments in the bile. The bile pigments are primarily responsible for the color of feces.

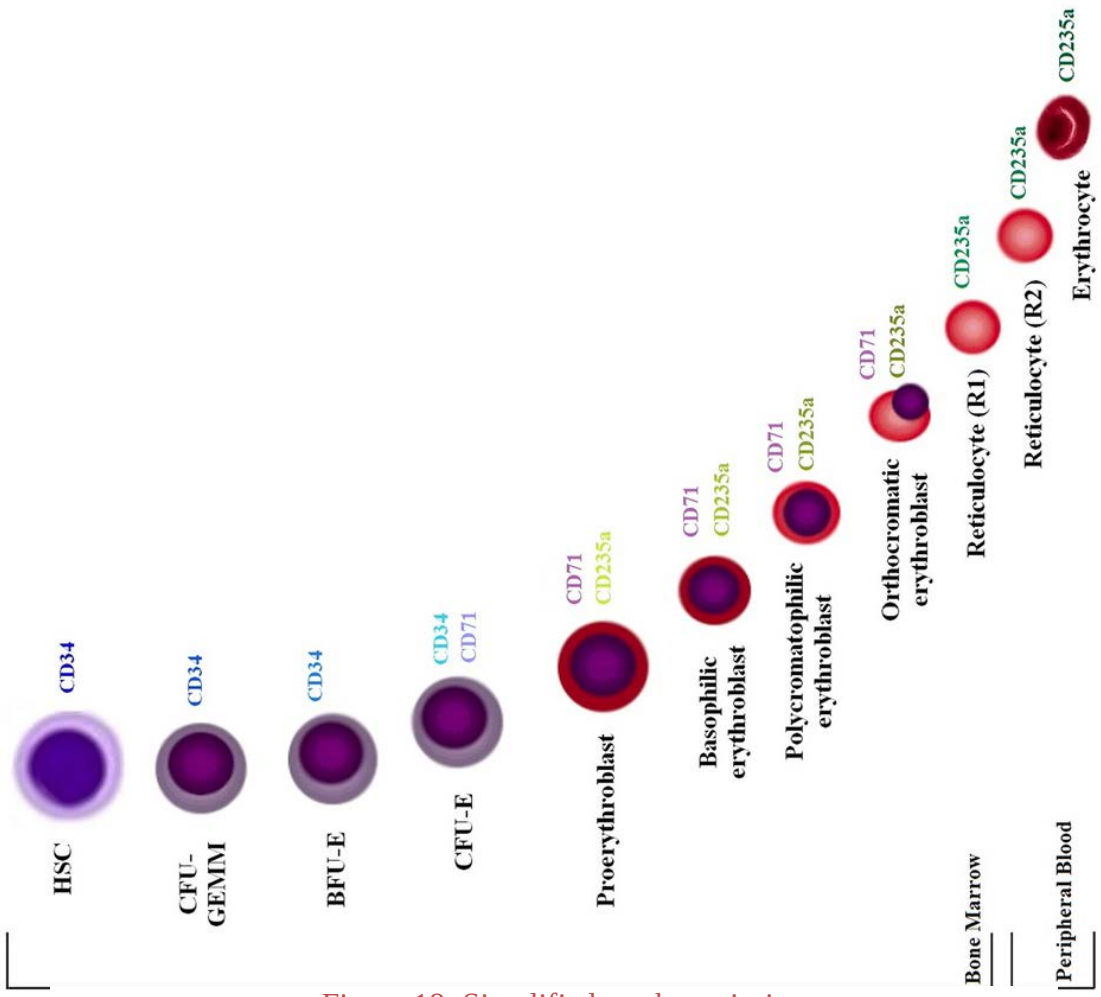

Figure 18: Simplified erythropoiesis

2.3.3. Red blood cell function

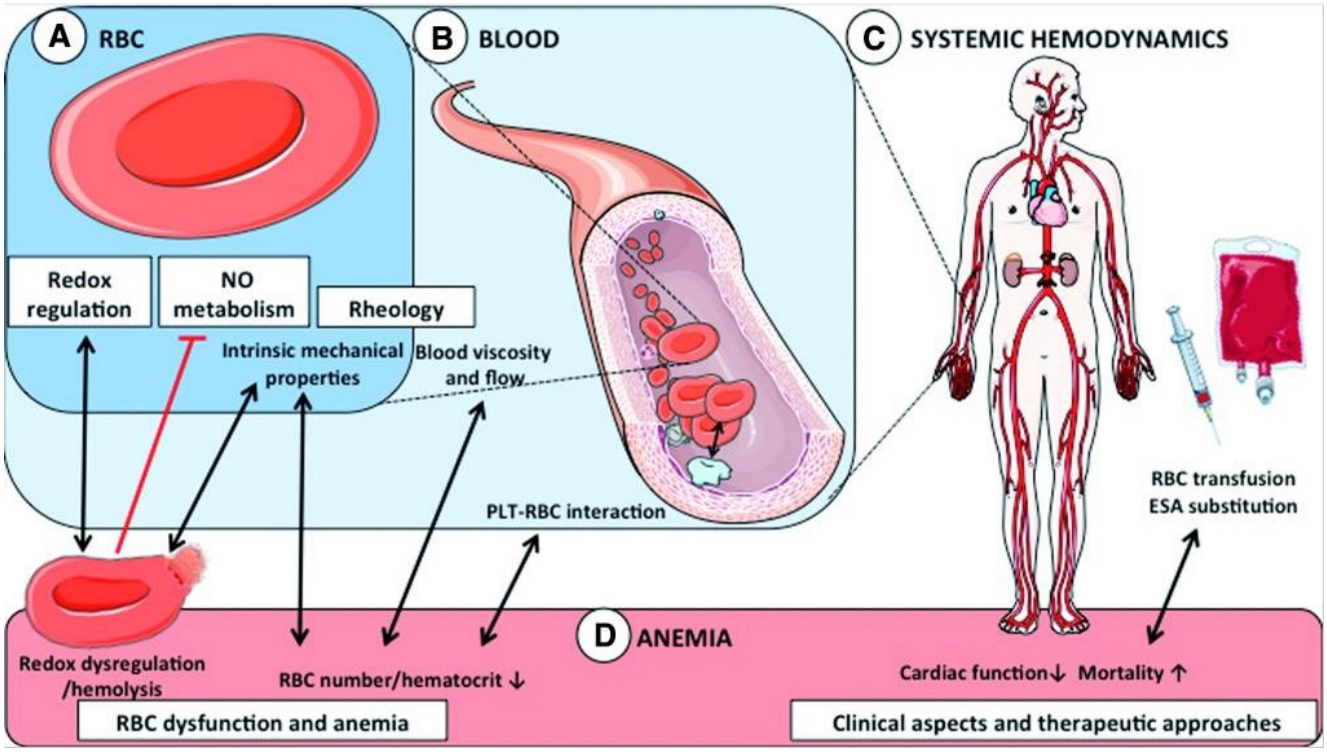

Figure 20: RBC function and dysfunction: redox regulation, NO metabolism, and anemia

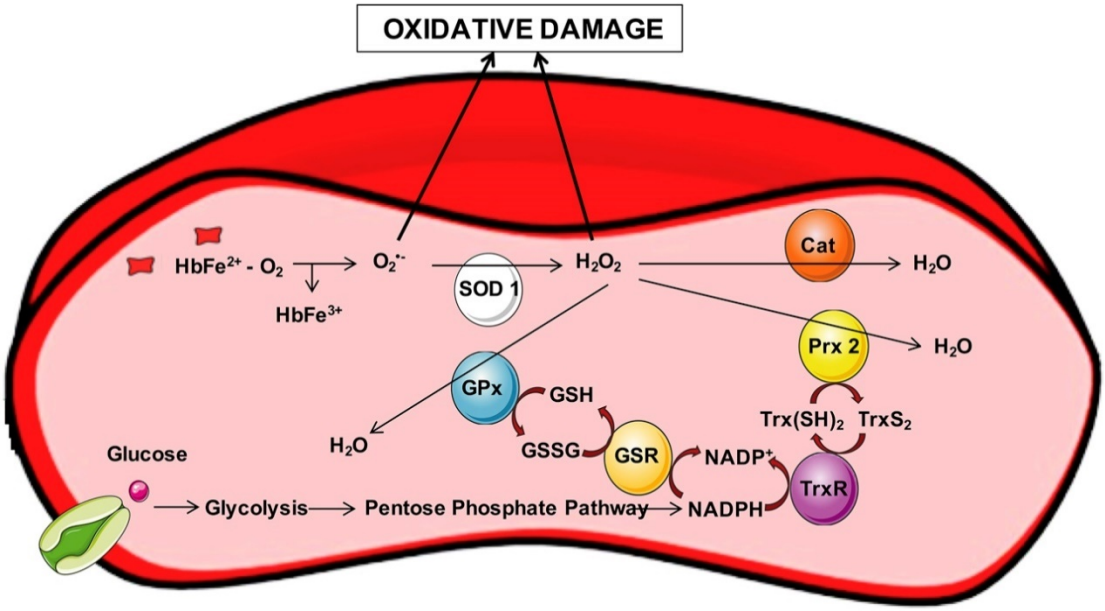

Figure 19: Erythrocyte metabolic function

(A) (figure 19) Intrinsic RBC properties and function. Beside their canonical role in transport of gases and nutrients, RBCs are well equipped with redox buffer systems and are important modulators of NO (Nitric oxide) metabolism. Their intrinsic mechanical properties allow them to deform/change their shape in response to changes in flow and to changes in vessel diameter, thus participating in control of blood rheology. (B) Effects of RBCs in blood. A second way for RBCs to control blood rheology is via their concentration (hematocrit), which critically defines blood viscosity and blood rheology. In addition, RBCs interact with PLTs resulting in a complex cell–cell communication involving membrane adhesion molecules, NO metabolism, and redox regulation. (C) Effects on systemic hemodynamics. In addition to control of vascular tone and cardiac function, intrinsic RBC properties and overall blood rheology are contributors to systemic vascular hemodynamics. (D) Anemia. RBC dysfunction mainly results in a number of anemic conditions, which are characterized by a decrease in blood Hb concentration and circulating number of RBCs. Redox dysregulation results mainly in hemolytic anemia and release of Hb, affecting redox metabolism and NO scavenging. Anemia affects systemic hemodynamics and myocardial performance. Furthermore, patients with Cardiovascular Diseases (CVD) show disturbances in hemostasis and thromboembolism and increased mortality, which cannot be effectively treated by blood transfusion or substitution of ESAs.

II. Blood group systems

1. Surface markers on the red blood cell membrane (Blood group antigens)

Before the 1900s, it was thought that all blood was the same, a misunderstanding that led to frequently fatal transfusions of animal blood into humans and hazardous transfusions of blood between people. Human blood is not the same; people belong to different blood groups, depending upon the surface markers found on the red blood cell.

The cells that make up the body tissues and organs are covered with surface markers, or antigens. Red blood cells are no different. This part of the thesis will describe the types of red blood cell antigen and explain why they are so important in medicine today.

1.1. Blood group antigens biochemical nature and function

Blood group antigens are either sugars or proteins, and they are attached to various components in the red blood cell membrane. For example, the antigens of the ABO blood group are sugars. They are produced by a series of reactions in which enzymes catalyze the transfer of sugar units. A person's DNA determines the type of enzymes they have, and, therefore, the type of sugar antigens that end up on their red blood cells. In contrast, the antigens of the Rh blood group are proteins. A person's DNA holds the information for producing the protein antigens. The RhD gene encodes the D antigen, which is a large protein on the red blood cell membrane. Some people have a version of the gene that does not produce D antigen, and therefore the RhD protein is absent from their red blood cells.

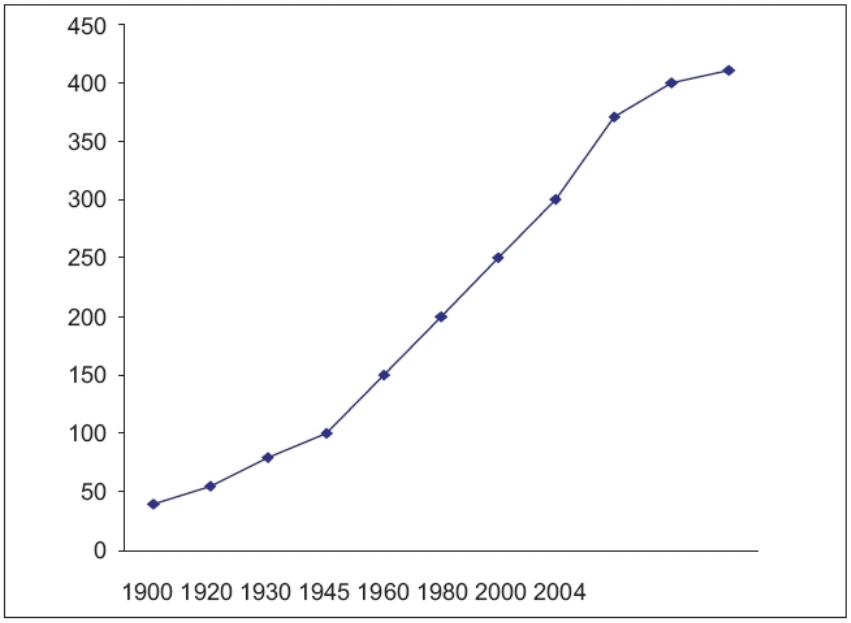

Figure 21: Number of red blood cell antigens known, year by year

The antigens expressed on the red blood cell determine an individual's blood group.

The functions of many of the blood group antigens are not known, and the theories about them having anti-pathologies effects are still going. But the presence or absence of red blood cell antigens becomes extremely important when blood from different people mixes, for instance, when a patient receives a blood transfusion from a blood bank. This also happens when a mother becomes pregnant because during labor, a small amount of fetal blood enters her circulation. In these circumstances, exposure to the foreign antigens on the red blood cells can trigger immune reactions. It is not possible to completely remove the danger of adverse reactions when blood from two people mix, but the danger can be minimized. Before a blood transfusion takes place, the blood to be donated must be "typed and cross matched" with the patient's blood to ensure immune compatibility. In pregnancy, the risk of the mother's immune system attacking the foreign antigens present on her fetus red blood cells is prevented by giving the mother antibodies _called RhoGAM serum injection or anti-D_ to cover fetal red blood cell antigens and removing them from the mother's circulation before her immune cells find them.

1.2. Biosynthesis of antigens of some blood group systems

Synthesis of blood group antigens needs at least two steps. The first is the synthesis of H antigen, the structure corresponding to O blood type. The second is the synthesis of either A or B structure. The H antigen is formed by the addition of fucose in α1,2 linkage to a terminal galactose on a type 1-4 chain. After synthesis of the H structure, the A and B transferases, which differ by four amino acids, utilize the H structure to synthesize A and B antigens on type 1-4 chains. Two genetic loci encode the H transferase. The H loci is functional in RBCs and the secretor loci is functional in GI epithelial cells, obtaining its name for the blood group antigens produced by secreted glycoconjugates.

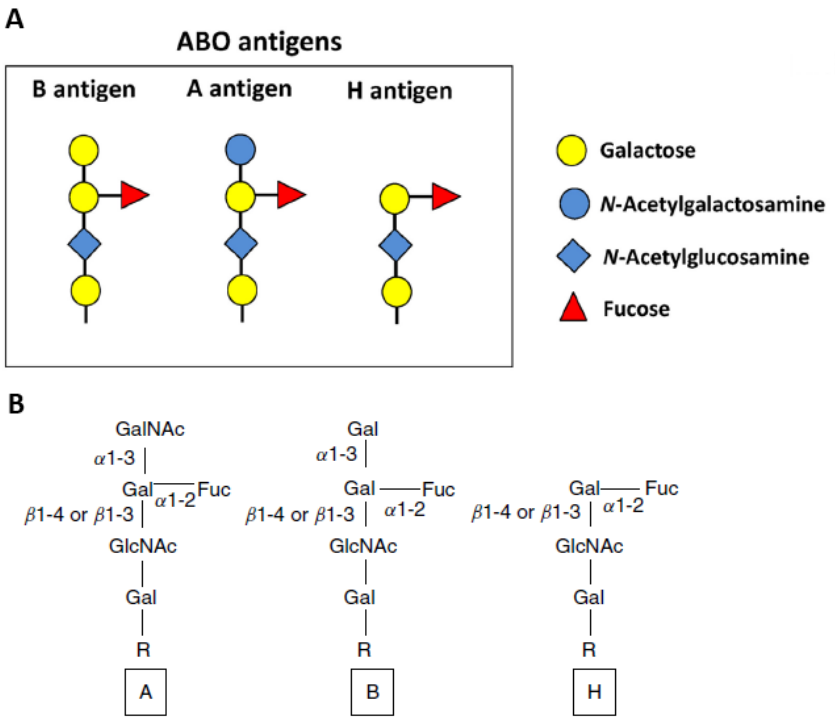

Figure 22: ABO blood group antigens

2. Blood group systems

The term "blood group" refers to the entire blood group system comprising red blood cell (RBC) antigens whose specificity is controlled by a series of genes which can be allelic or linked very closely on the same chromosome. "Blood type" refers to a specific pattern of reaction to testing antisera within a given system. Over a period of time, our understanding on blood groups has evolved to encompass not only transfusion-related problems but also specific disease association with RBC surface antigens. Karl Landsteiner has been credited for the discovery of ABO blood group system in 1900. His extensive research on serology based on simple but strong scientific reasoning led to identification of major blood groups such as O, A, and B types, compatibility testing, and subsequent transfusion practices. He was awarded Noble Prize in 1930 for this discovery. His obituary lists an immense contribution of more than 346 publications. Later, Jan Jansky described classification of human blood groups of four types, O, A, B and AB.

2.1. Blood group genetics

Blood group genetics are concerned with the way in which the different blood groups are inherited, that is passed on from parents to children.

2.2. ABO blood group system

a. History

At the beginning of the 20th century an Austrian scientist, Karl Landsteiner, noted that the RBCs of some individuals were agglutinated by the serum from other individuals. He made a note of the patterns of agglutination and showed that blood could be divided into groups. This marked the discovery of the first blood group system, ABO, and earned Landsteiner a Nobel Prize.

Landsteiner explained that the reactions between the RBCs and serum were related to the presence of markers (antigens) on the RBCs and antibodies in the serum. Agglutination occurred when the RBC antigens were bound by the antibodies in the serum. He called the antigens A and B, and depending upon which antigen the RBC expressed, blood either belonged to blood group A or blood group B. A third blood group contained RBCs that reacted as if they lacked the properties of A and B, and this group was later called "O" after the German word "Ohne", which means "without". The following year the fourth blood group, AB, was added to the ABO blood group system. These RBCs expressed both A and B antigens.

In 1910, scientists proved that the RBCs antigens were inherited, and that the A and B antigens were inherited co-dominantly over O. There was initially some confusion over how a person's blood type was determined, but the puzzle was solved in 1924 by Bernstein's "three allele model".

The ABO blood group antigens are encoded by one genetic locus, the ABO locus, which has three alternative (allelic) forms—A, B, and O. A child receives one of the three alleles from each parent, giving rise to six possible genotypes and four possible blood types (phenotypes).

b. Basic biochemistry

ABO phenotypes

The four basic ABO phenotypes are O, A, B, and AB. After it was found that blood group A RBCs reacted differently to a particular antibody (later called anti-A1), the blood group was divided into two phenotypes, A1 and A2. RBCs with the A1 phenotype react with anti-A1 and make up about 80% of blood type A. RBCs with the A2 phenotype do not react with anti-A1 and they make up about 20% of blood type A. A1 red cells express about 5 times more A antigen than A2 red cells, but both types of red cell react with anti-A, and as far as transfusion purposes are concerned, the A1 and A2 blood groups are interchangeable. There are many other subgroups of blood group A in which RBCs tend to weakly express the A antigen, whereas weak variants of the blood group B phenotype are rare.

The immune system forms antibodies against whichever ABO blood group antigens are not found on the individual's RBCs. Thus, a group A individual will have anti-B antibodies and a group B individual will have anti-A antibodies. Blood group O is common, and individuals with

this blood type will have both anti-A and anti-B in their serum. Blood group AB is the least common, and these individuals will have neither anti-A nor anti-B in their serum.

ABO antibodies in the serum are formed naturally. Their production is stimulated when the immune system encounters the "missing" ABO blood group antigens in foods or in micro-organisms. This happens at an early age because sugars that are identical to, or very similar to, the ABO blood group antigens are found throughout nature.

The ABO locus has three main allelic forms: A, B, and O. The A allele encodes a glycosyltransferase that produces the A antigen (N-acetylgalactosamine is its immunodominant sugar), and the B allele encodes a glycosyltransferase that creates the B antigen (D-galactose is its immunodominant sugar).

The O allele encodes an enzyme with no function, and therefore neither A or B antigen is produced, leaving the underlying precursor (the H antigen) unchanged. These antigens are incorporated into one of four types of oligosaccharide chain, type 2 being the most common in the antigen-carrying molecules in RBC membranes. Some of the other enzymes involved in the earlier stages of ABO antigen synthesis are also involved in producing antigens of the Hh blood group and the Lewis blood group.

Expression

Although the ABO blood group antigens are regarded as RBC antigens, they are actually expressed on a wide variety of human tissues and are present on most epithelial and endothelial cells.

Each human RBC expresses about 2 million ABO blood group antigens. Other blood cells, such as T cells, B cells, and platelets, have ABO blood group antigens that have been adsorbed from the plasma. In individuals who are "secretors", a soluble form of the ABO blood group antigens is found in saliva and in all bodily fluids except for the cerebrospinal fluid.

A number of illnesses may alter a person's ABO phenotype. Patients can "acquire" the B antigen during a necrotizing infection during which bacteria release an enzyme into the circulation that converts the A1 antigen into a B-like antigen. During this time, patients should not receive blood products that contain the B antigen because their sera will still contain anti-B. Once the underlying infection is treated, the patients' blood groups return to normal. Illness can also cause patients to "lose" ABO blood group antigens. Any disease that increases the body's demand for RBCs may weaken the expression of ABO blood group antigens, e.g., thalassemia. In addition, ABO blood group antigens can be altered by hematological cancers that can modify the sugar chains that bear the ABO blood group antigens, lending to the use of the A and B antigens as tumor markers for acute leukemia, myeloproliferative disorders, and myelodysplasia.

Clinical significance of ABO antibodies

ABO antibodies are of major clinical significance for two reasons: they are naturally occurring and are found universally, and, they are highly reactive.

Transfusion reactions

The routine practice of blood typing and cross matching blood products should prevent adverse transfusion reactions caused by ABO antibodies. However, clerical error can result in "the wrong blood" being transfused into a patient, an error which can result in the death of the patient. If a recipient who has blood group O is transfused with non-group O RBCs, the naturally occurring anti-A and anti-B in the recipient's serum binds to their corresponding antigens on the transfused RBCs. These antibodies fix complement and cause rapid intravascular hemolysis, triggering an acute hemolytic transfusion reaction that can cause disseminated intravascular coagulation, shock, acute renal failure, and death. Anti-A1 is a less significant cause of transfusion reactions and does not appear to fix complement.

c. Molecular information

Gene

The ABO locus encodes specific glycosyltransferases that synthesize A and B antigens on RBCs. For A/B antigen synthesis to occur, a precursor called the H antigen must be present. In RBCs, the enzyme that synthesizes the H antigen is encoded by the H locus (FUT1). In saliva and other bodily secretions, the enzyme that synthesizes the H antigen is encoded by the Se locus (FUT2).

The ABO locus

The ABO locus is located on chromosome 9 at 9q34.1-q34.2. It contains 7 exons that span more than 18 kb of genomic DNA. Exon 7 is the largest and contains most of the coding sequence. Exon 6 contains the deletion that is found in most O alleles and results in a loss of enzymatic activity.

The A and B alleles differ from each other by seven nucleotide substitutions, four of which translate into different amino acids in the gene product (R176G, G235S, L266M, G268A). The residues at positions 266 and 268 determine the A or B specificity of the glycosyltransferase they encode. The O allele differs from the A allele by deletion of guanine at position 261. The deletion causes a frameshift and results in translation of an almost entirely different protein that lacks enzymatic activity. There are many variant ABO alleles that encode a number of variant ABO phenotypes, but they do not encode specific antigens other than the A and B antigens. For example, weak A subgroups, such as A3, Ax, and Ael, express the A antigen, and weak B subgroups, such as B3 and Bx, express the B antigen.

The H locus (FUT1)

The H locus is located on chromosome 19 at 19q13.3. It contains three exons that span more than 5 kb of genomic DNA, and it encodes a fucosyltransferase that produces the H antigen on RBCs.

Individuals who are homozygous for null alleles at this locus (h/h) do not produce H antigen, and because the H antigen is an essential precursor to the ABO blood group antigens, they cannot produce A and B antigens. Therefore, their serum contains anti-A and anti-B, in addition to potent anti-H. This rare phenotype of H-deficient RBCs is called the "Bombay phenotype" (Oh) after the city in which it was first discovered. Individuals with the Bombay phenotype are healthy, but if they ever needed a blood transfusion, the antibodies in their serum would place them at a high risk of having an acute hemolytic transfusion reaction. This can be avoided by using only blood products from a donor who also has the Bombay phenotype (usually a relative).

The Se locus (FUT2)

The Se locus is located on chromosome 19 at 19q13.3. It contains two exons that span about 25 kb of genomic DNA.

The Se locus encodes a specific fucosyl transferase that is expressed in the epithelia of secretory tissues, such as salivary glands, the gastrointestinal tract, and the respiratory tract. The enzyme it encodes catalyzes the production of H antigen in bodily secretions. "Secretors" have at least one copy of the Se gene that encodes a functional enzyme—their genotype is Se/Se or Se/se. They secrete H antigen which, depending on their ABO genotype, is then processed into A and/or B antigens. Non-secretors are homozygous for null alleles at this locus (se/se). They are unable to produce a soluble form of H antigen and hence do not produce A and B antigens.

2.3. Rh blood group system

a. History

In 1939, a mother who had just given birth to a still-born child needed a blood transfusion. The ABO blood group system had been discovered almost 40 years previously, and the importance of giving an ABO-compatible blood transfusion was well established. However, although the mother was transfused with ABO compatible blood from her husband, she still experienced an adverse reaction to the transfusion. Her serum was found to contain antibodies that agglutinated her husband's RBCs, even though they were ABO compatible. The death of the mother's fetus and her adverse reaction to a blood transfusion from her husband was related. During the pregnancy, the mother had been exposed to an antigen on the fetal RBCs that was of paternal origin. Her immune system attacked this antigen, and the destruction of the fetal RBCs resulted in fetal death. The mother re-encountered the same paternal antigen when she received a blood transfusion from her husband. This time her immune system attacked the transfused RBCs, causing a hemolytic transfusion reaction. The antibodies responsible led to the discovery of the Rh blood group.

It was wrongly thought that the agglutinating antibodies produced in the mother's serum in response to her husband's RBCs were the same specificity as antibodies produced in various animals' serum in response to RBCs from the Rhesus monkey. In error, the paternal antigen was named the Rhesus factor. By the time it was discovered that the mother's antibodies were produced against a different antigen, the rhesus blood group terminology was being widely used. Therefore, instead of changing the name, it was abbreviated to the Rh blood group.

Remarkably, only 20 years after the discovery of Rh incompatibility in pregnancy, effective treatment became available. Today, the Rh status of mothers-to-be is checked during pregnancy to identify those at risk of HDN. In addition, all blood transfusions are matched for the Rh status.

b. Basic biochemistry

Common Rh phenotypes

The most common Rh haplotype in Caucasians, Asians, and Native Americans is Dce. In Blacks, the Dce haplotype is slightly more common. In Caucasians, the Rh D-negative phenotype results from a deletion of the RHD gene. About 15% of Caucasians are Rh D-negative. In Africans, there are three molecular backgrounds that give rise to the Rh D-phenotype which is found in 8% of the population. One is the RHD gene deletion that is common in Caucasians. The other two mechanisms are inheriting a RHD pseudogene (contains a duplication of nucleotides that introduces a premature stop codon) or inheriting a RHD hybrid gene (contains nucleotide sequences from the RHCE gene, produces no D antigen and abnormal C antigen).

Uncommon Rh phenotypes

The D antigen contains over 30 epitopes. Variations of the D phenotype arise when these epitopes are only weakly expressed ("weak D phenotype") or when some are missing ("partial D phenotype").

Weak D (all D antigen epitopes are present but are underexpressed): "Weak D" is a Rh phenotype found in less than 1% of Caucasians and is only slightly more common in African Americans. It is typically caused by a single amino acid switch in the transmembrane region of the RhD protein. This disrupts how the RhD protein is inserted into the RBC membrane, reducing the level of expression of RhD. In most cases, adequate levels of D antigen are present and because there has been no change in D epitopes, the formation of anti-D is prevented. Therefore, individuals with the weak D phenotype can receive Rh D-positive blood.

Partial D (some D antigen epitopes are missing): In contrast, people who have been identified as having the "partial D" phenotype should not receive Rh D-positive blood but in practice, people with partial D are difficult to identify. This phenotype is usually caused by the creation of a hybrid RhD and RhCE protein. The hybrid protein is similar enough to RhD to be correctly inserted in the RBC membrane, but it lacks several epitopes found on the complete RhD protein.

If a person with the partial D phenotype encounters the complete D antigen on transfused RBCs, they may form anti-D and suffer from a transfusion reaction.

Expression of Rh antigens

The Rh antigens are expressed as part of a protein complex in the RBC membrane. This complex is only expressed in cells of the erythroid line, and therefore Rh antigens are only expressed in RBCs. The composition of the complex is unknown, but it is thought to be a tetramer, consisting of two molecules of Rh-associated glycoprotein (RhAG) and two molecules of Rh proteins. The Rh proteins may be RhD (carrying the D antigen) or RhCE (carrying the C or c antigen and the E or e antigen). It is unknown whether both RhCE and RhD can be in a single complex, but in D-negative individuals the complex would only contain RhCE.

RhAG must be present to direct the Rh antigens to the RBC membrane. If it is missing, none of the Rh antigens are expressed. RHAG is related to the Rh proteins, sharing about 35% of their primary sequence and is the same type of transmembrane protein. However, it is not polymorphic and does not carry Rh antigens itself.

Function of Rh proteins

The Rh antigens are thought to play a role in maintaining the integrity of the RBC membrane—RBCs which lack Rh antigens have an abnormal shape.

Individuals with the rare Rhnull phenotype caused by the deletion of RHAG have RBCs that do not express any of the Rh antigens because they cannot be targeted to the RBC membrane. The absence of the Rh complex alters the RBC shape, increases its osmotic fragility, and shortens its lifespan, resulting in a hemolytic anemia that is usually mild in nature. These patients are at risk of adverse transfusion reactions because they may produce antibodies against several of the Rh antigens. Rh antigens may also be involved in the transport of ammonium across the RBC membrane. Interestingly, the first member of a family of water channels (aquaporins) and the first member of a family of urea transporters were both found in blood group proteins (the Colton blood group and Kidd blood group, respectively).

Clinical significance of Rh antibodies

The Rh antigens are highly immunogenic, and most of the Rh antibodies should be considered as potential causes of hemolytic transfusion reactions and HDN.

Whereas most blood types are determined by red cell antigens that differ by one or two amino acids, the Rh blood group contains the D antigen which differs from the C/c and E/e antigens by 35 amino acids. This large difference in amino acids is the reason why the Rh antigens are potent at stimulating an immune response. The majority of antibodies formed against the Rh antigens are of the IgG type. They are capable of causing significant HTR and

HDN. Rh antibodies rarely, if ever, bind complement, and therefore RBC destruction is mediated almost exclusively via macrophages in the spleen (extravascular hemolysis).

There are a few examples of Rh alloantibodies that are naturally occurring and are of the IgM type, but they are in the minority.

c. Molecular information

Gene

The Rh locus is located on the long arm of chromosome 1 (on 1p36-p34). It contains the RHD and RHCE genes, which lie in tandem. The RHD and RHCE genes are structural homologs and result from a duplication of a common gene ancestor. RHD and RHCE each contain 10 exons and span a ~75-kb DNA sequence. The RHD gene is flanked by two 9-kb, highly homologous sequences called "Rhesus boxes". It is thought that unequal homologous recombination confined to the Rhesus boxes is a common cause of the deletion of the RHD gene, which is found in up to 40% of the population.

2.4. Hh blood group system

a. History

In Bombay, India, an individual was discovered to have an interesting blood type that reacted to other blood types in a way that had not been seen before. Serum from this individual contained antibodies that reacted with all RBCs from normal ABO phenotypes (i.e., groups O, A, B, and AB). The individual's RBCs appeared to lack all of the ABO blood group antigens plus an additional antigen that was previously unknown.

In 1952, a paper about the "new blood group character related to the ABO blood group" was published. This new blood group character is the H antigen and it is the building block for the antigens of the ABO blood group. Named for the city in which it was first discovered, the "Bombay phenotype" describes individuals whose RBCs lack the H antigen. Because the A and B antigens cannot be formed without the H antigen precursor, their RBCs also lack these antigens. As a result, these individuals produce anti-H, anti-A, and anti-B and can therefore be transfused only with RBCs that also lacks the H, A, and B antigens i.e., they can only receive blood from another person with the Bombay phenotype. Because of the rarity of this blood type, this normally means using blood donations from a suitable relative.

b. Basic biochemistry

The biosynthesis of the H antigen and the A and B antigens involves a series of enzymes (glycosyltransferases) that transfer monosaccharides. The resulting antigens are oligosaccharide chains, which are attached to lipids and proteins that are anchored in the RBC membrane.

The H antigen is produced by a specific fucosyl transferase. Depending upon a person's ABO blood type, the H antigen is converted into either the A antigen, B antigen, or both. If a person has blood group O, the H antigen remains unmodified. Therefore, the H antigen is present in the highest amounts in blood type O and in the least amounts in blood type AB. Two regions of the genome encode two enzymes with very similar substrate specificities—the H locus (FUT1) and the Se locus (FUT2). The H locus contains the FUT1 gene, which is expressed in RBCs. At least one functioning copy of FUT1 needs to be present (H/H or H/h) for the H antigen to be produced on RBCs. If both copies of FUT1 are inactive (h/h), the Bombay phenotype results. The Se locus contains the FUT2 gene, which is expressed in secretory glands. Individuals who are "secretors" (Se/Se or Se/se) contain at least one copy of a functioning enzyme. They produce a soluble form of H antigen that is found in saliva and other bodily fluids. "Non-secretors" (se/se) do not produce soluble H antigen. The enzyme encoded by FUT2 is also involved in the synthesis of antigens of the Lewis blood group.

Common H phenotypes

The two common H phenotypes are "secretor" and "non-secretor"; Secretor (common) such as H antigen, is expressed on RBCs. H antigen is expressed in saliva. No anti-H is produced.

Genotype: H/H or H/h; Se/Se or Se/se

Non secretor (common), for example, H antigen, is present on RBCs. H antigen is absent from saliva. No anti-H is produced.

Genotype: H/H or H/h; se/se

Uncommon H Phenotypes

The Bombay phenotype and para-Bombay phenotype are relatively rare. In India, where H deficiency was first discovered, the frequency of both phenotypes combined is 1 in 10,000. H deficiency is slightly more common in Taiwan, affecting 1 of 8,000 people. A relatively large number of H-deficient individuals were found on Reunion Island, which is a small French Island 800 km east of Madagascar in the Indian Ocean. Both the classical Bombay phenotype and a new variant type of partial H deficiency was seen in the islanders. In Europe, 1 per million people are H deficient.

Expression of the H antigen

The H antigen shares the same broad tissue distribution as the A and B antigens. Likewise, in individuals who are "secretors", a soluble form of the H antigen is found in saliva and all fluids except cerebrospinal fluid.

Function of the H antigen

The function of the H antigen, apart from being an intermediate substrate in the synthesis of ABO blood group antigens, is not known although it may be involved in cell adhesion. People who lack the H antigen do not suffer any deleterious effects, and being H-deficient is only an issue if they were to need a blood transfusion because they would require H-deficient blood.

Clinical significance of H antibodies

Transfusion reactions

If patients with anti-H in their circulation receive transfusions of blood that contains the H antigen (e.g., blood group O), they are at risk of suffering an acute hemolytic transfusion reaction.

c. Molecular information

The H blood group locus (containing FUT1) and the secretor locus (containing FUT2) are located on chromosome 19 at q.13.3. FUT1 and FUT2 are tightly linked, being only 35 kb apart. Because they are highly homologous, they are likely to have been the result of a gene duplication of a common gene ancestor.

The H locus contains four exons that span more than 8 kb of genomic DNA. Both the Bombay and para-Bombay phenotypes are the result of point mutations in the FUT1 gene.

The classical Bombay phenotype is caused by a Tyr316Ter mutation in the coding region of FUT1. The mutation introduces a stop codon, resulting in a truncated enzyme that lacks 50 amino acids at the C-terminal end, rendering the enzyme inactive. In Caucasians, the Bombay phenotype may be caused by a number of mutations. Likewise, a number of mutations have been reported to underlie the para-Bombay phenotype

Chapter 3: cardiovascular diseases and its relationship with ABO blood group system

I. Cardiology

1. A brief history of cardiology

"The heart… is the beginning of life; the sun of the microcosm… for it is the heart by whose virtue and pulse the blood is moved, perfected, made apt to nourish, and is preserved from corruption and coagulation; it is the household divinity which, discharging its function, nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action." —William Harvey, 1628

Cardiology [Gk. kardia, heart, and Gk. logos, science] is a branch of medicine that concerns diseases and disorders of the heart, which may range from congenital defects through to acquired heart diseases such as coronary artery disease and congestive heart failure.

Thought at one time to be the center of the soul and impervious to disease, the heart was long a source of mystery and wonder, studied in science and fascinated about in literature and the arts. Most historians agree that William Harvey's discovery of the circulation of blood in the early 17th century is a good place to start the modern history of cardiovascular medicine. Following Harvey, cardiology pursued a pathway of descriptive anatomy and pathology in the 17th and 18th centuries, auscultation and its correlations in the 19th century, an understanding of cardiac disease and its pathophysiology in the second half of the 19th and first half of the 20th centuries, and major advances in the diagnosis and treatment of heart disease from there into the 21st century.

Table 2: Historical timeline of major events in cardiology discipline

Year	Event
1628	The circulation of blood was described by an English Physician William Harvey
1706	A French anatomy professor, Raymond de Vieussens, described the structure of the heart's chambers and vessels.
1733	Blood pressure was first measured by an English clergyman and scientist called Stephen Hales.
1816	A French physician, Rene Laennec, invented the stethoscope.
1903	A Dutch physiologist Willem Einthoven, developed the electrocardiograph or ECG, a vital instrument used to measure the electrical activity of the heart and diagnose heart abnormalities.
1912	An American physician, James Herric, described atherosclerosis – one of the most common diseases of the heart.
1938	Robert Gross, an American surgeon, performed the first heart surgery
1951	The first artificial heart valve was developed by Charles Hufnagel.

1952	An American surgeon called Floyd John Lewis performed the first open heart surgery
1967	Christian Barnard, a South African surgeon, performed the first whole heart transplant
1982	An American surgeon called Willem DeVries implanted a permanent artificial heart designed by Robert Jarvik, into a patient.

2. The heart

a. Anatomy of the heart

The heart is a muscular organ that pumps blood around the body by circulating it through the circulatory/vascular system. It is found in the middle mediastinum, wrapped in a two-layered serous sac called the pericardium. The heart is shaped as a quadrangular pyramid, and orientated as if the pyramid has fallen onto one of its sides so that its base faces the posterior thoracic wall, and its apex is pointed toward the anterior thoracic wall. The great vessels that originate from the heart, radiate their branches to the head and neck, the thorax and abdomen and the upper and lower limbs.

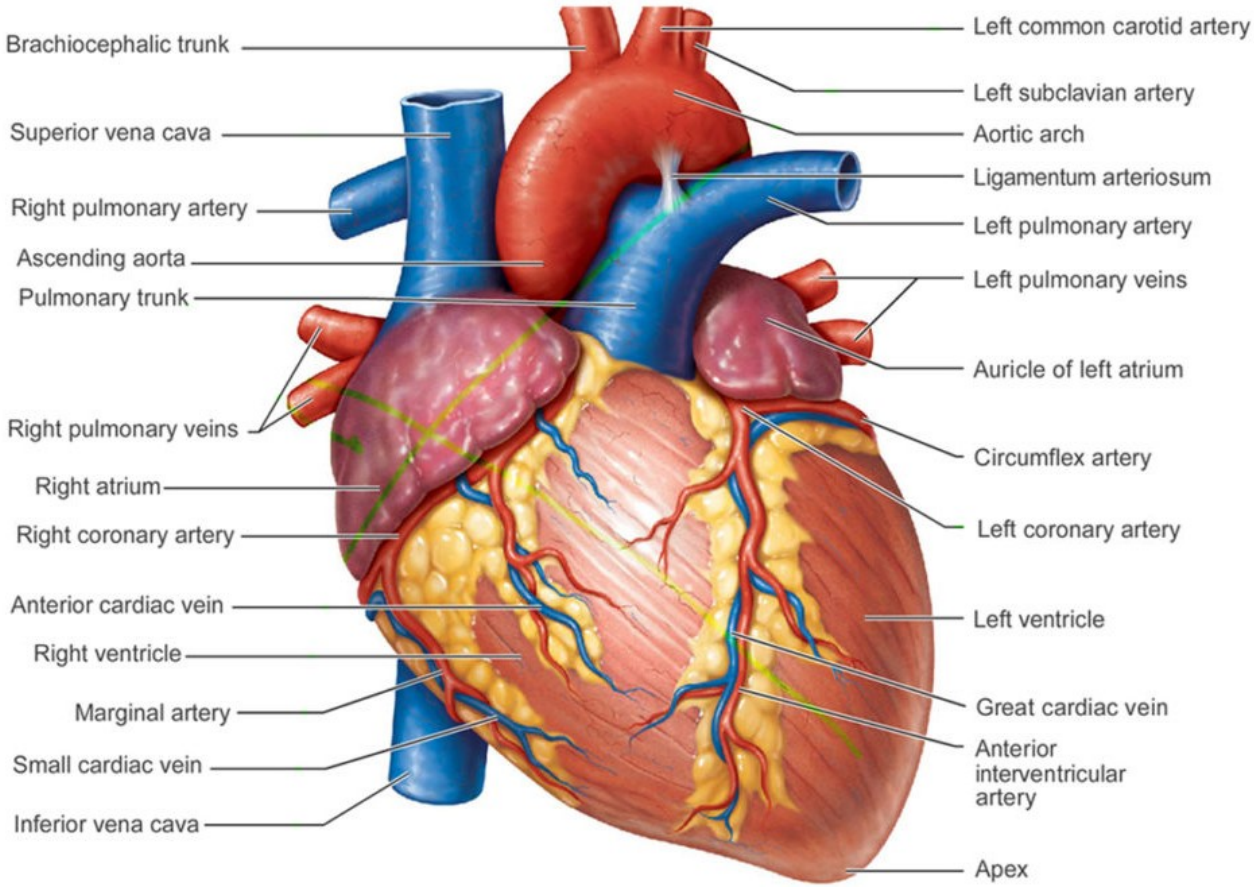

Figure 23: Anatomy of normal heart

b. Heart function

1. Blood circulation

The heart circulates blood through two pathways: **the pulmonary circuit** and **the systemic circuit**. In the pulmonary circuit, deoxygenated blood leaves the right ventricle of the heart via the pulmonary artery and travels to the lungs, then returns as oxygenated blood to the left atrium of the heart via the pulmonary vein. In the systemic circuit, oxygenated blood leaves the body via the left ventricle to the aorta, and from there enters the arteries and capillaries where it supplies the body's tissues with oxygen. Deoxygenated blood returns via veins to the venae cavae, re-entering the heart's right atrium. Of course, the heart is also a muscle, so it needs a fresh supply of oxygen and nutrients. The left main coronary artery, on one side of the aorta, branches into the left anterior descending artery and the left circumflex artery. The right coronary artery branches out on the right side of the aorta.

Blockage of any of these arteries can cause a heart attack, or damage to the muscle of the heart. A heart attack is distinct from cardiac arrest, which is a sudden loss of heart function that usually occurs as a result of electrical disturbances of the heart rhythm. A heart attack can lead to cardiac arrest, but the latter can also be caused by other problems.

The heart contains electrical "pacemaker" cells, which cause it to contract producing a heartbeat. In people with an irregular heartbeat, or atrial fibrillation, every cell tries to be the band leader, which causes them to beat out of sync with one another.

2. Blood flow

The blood flow through the heart is quite logical. It happens with the heart cycle, which consists of the periodical contraction and relaxation of the atrial and ventricular myocardium (heart muscle tissue). Systole is the period of contraction of the ventricular walls, while the period of ventricular relaxation is known as diastole. Note that whenever the atria contract, the ventricles are relaxed and vice versa. Let’s put into words the heart blood flow diagram:

- The right atrium receives deoxygenated blood from the superior and inferior venae cavae and coronary sinus
- The right atrium contracts pushing blood through the right atrioventricular valve into the right ventricle. The right ventricle then contracts passing the blood into the pulmonary trunk via the pulmonary valve to reach the lungs
- In the lungs, the blood gets oxygenated then moves back into the heart entering the left atrium through the pulmonary veins.
- The left atrium contracts and pushes the blood into the left ventricle through the left atrioventricular valve.

- The left ventricle pushes oxygenated blood through the aortic semilunar valve into the aorta, from which blood is distributed throughout the body.

The heart cycle is regulated completely subconsciously by an autonomic nerve plexus called the cardiac plexus.

The heart must also be supplied with oxygenated blood. This is done by the two coronary arteries: left and right.

Heart muscles work constantly, so the heart has a very high nutrient need. The coronary arteries arise from the aortic sinuses at the beginning of the ascending aorta, and then circle the heart–giving off several branches. In this way, oxygenated blood reaches every part of the heart. Venous blood from the heart is collected into the cardiac veins: middle, posterior, and small. They are all tributaries to coronary sinus–a large vessel that delivers deoxygenated blood from the myocardium to the right atrium.

c. Heart dysfunction

Heart disease refers to various types of conditions that can affect heart function. Heart disease is common both in the population at large but also in the population of working age. It is estimated that heart disease, including stroke and high blood pressure, is responsible for more costs than any other disease or injury. The cost in occupational terms of cardiovascular disease (CVD) is, however, harder to quantify but is likely to be similarly high. Heart disease can claim the ultimate cost as the most common cause of death.

Among cardiovascular diseases we can mention the next:

- Congenital heart disease: birth defects that affect normal development and functioning of the heart caused by malformations of the heart structure from birth
- Peripherical arterial disease: what affects vessels supplying arms and legs
- Coronary artery (atherosclerotic) heart disease that affects the arteries to the heart; coronary arteries supply blood to the heart muscle and coronary artery disease occurs when there is a buildup of cholesterol plaque inside the artery walls. Over time, this buildup of plaque may partially block the artery and decrease blood flow through it. A heart attack occurs when a plaque ruptures and forms a clot in the artery causing a complete blockage. That part of the heart muscle that is denied blood supply starts to die.
- Valvular heart disease that affects how the valves function to regulate blood flow in and out of the heart
- Cardiomyopathy that affects how the heart muscle squeezes
- Heart rhythm disturbances (arrhythmias) that affect the electrical conduction
- Heart infections where the heart has structural problems that develop before birth

As for High Blood Pressure (HBP) is one of the most important risk factors for cardiovascular disease (CVD), which is the leading cause of mortality.

3. Cardiovascular system

The cardiovascular system is sometimes called the blood-vascular, or simply the circulatory, system. It consists of the heart, and a closed system of vessels called arteries, veins, and capillaries. As already mentioned; blood contained in the circulatory system is pumped by the heart around a closed circle or circuit of vessels as it passes again and again through the various "circulations" of the body.

As in the adult, survival of the developing embryo depends on the circulation of blood to maintain homeostasis and a favorable cellular environment. In response to this need, the cardiovascular system makes its appearance early in development and reaches a functional state long before any other major organ system.

The vital role of the cardiovascular system in maintaining homeostasis depends on the continuous and controlled movement of blood through the thousands of miles of capillaries that permeate every tissue and reach every cell in the body. It is in the microscopic capillaries that blood performs its ultimate transport function. Nutrients and other essential materials pass from capillary blood into fluids surrounding the cells as waste products are removed.

Blood vessels

Blood vessels are the channels or conduits through which blood is distributed to body tissues. The vessels make up two closed systems of tubes that begin and end at the heart. The pulmonary vessels and the system vessels system (review Heart function page 61). Based on their structure and function, blood vessels are classified as either arteries, capillaries, or veins.

a. Arteries

Arteries carry blood away from the heart. Pulmonary arteries transport blood that has a low oxygen content from the right ventricle to the lungs. Systemic arteries transport oxygenated blood from the left ventricle to the body tissues.

Blood is pumped from the ventricles into large elastic arteries that branch repeatedly into smaller and smaller arteries until the branching results in microscopic arteries called arterioles. The arterioles play a key role in regulating blood flow into the tissue capillaries.

The wall of an artery consists of three layers. The innermost layer, the tunica intima (also called tunica interna), is simple squamous epithelium surrounded by a connective tissue basement membrane with elastic fibers. The middle layer, the tunica media, is primarily smooth muscle and is usually the thickest layer. It not only provides support for the vessel but also changes vessel diameter to regulate blood flow and blood pressure. The outermost layer, which attaches the vessel to the surrounding tissue, is the tunica externa or tunica adventitia. This layer is connective tissue with varying amounts of elastic and collagenous fibers. The connective tissue in this layer is quite dense where it is adjacent to the tunic media, but it changes to loose connective tissue near the periphery of the vessel.

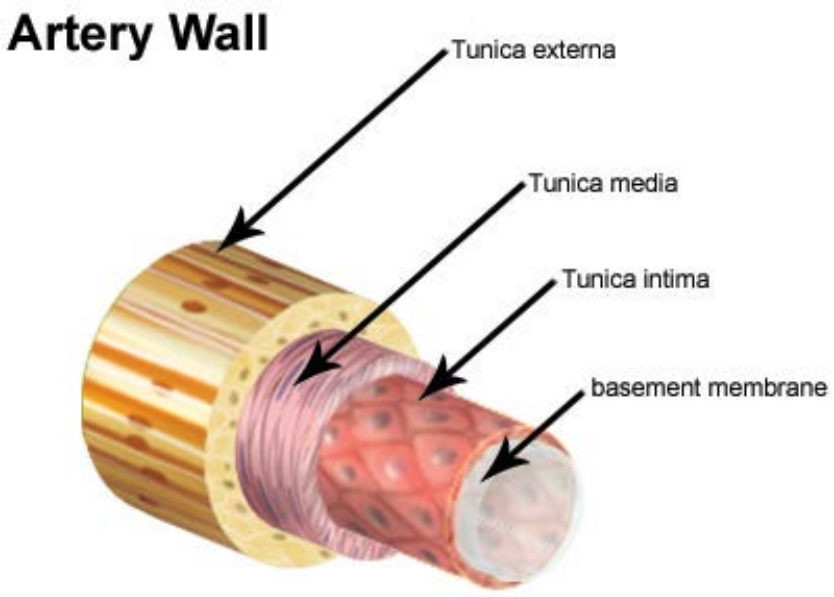

Figure 24: Artery wall

b. Capillaries

Capillaries, the smallest and most numerous of the blood vessels, form the connection between the vessels that carry blood away from the heart (arteries) and the vessels that return blood to the heart (veins).

The primary function of capillaries is the exchange of materials between the blood and tissue cells.

Capillary distribution varies with the metabolic activity of body tissues. Tissues such as skeletal muscle, liver, and kidney have extensive capillary networks because they are metabolically active and require an abundant supply of oxygen and nutrients. Other tissues, such as connective tissue, have a less abundant supply of capillaries. The epidermis of the skin and the lens and cornea of the eye completely lack a capillary network. Smooth muscle cells in the arterioles where they branch to form capillaries regulate blood flow from the arterioles into the capillaries.

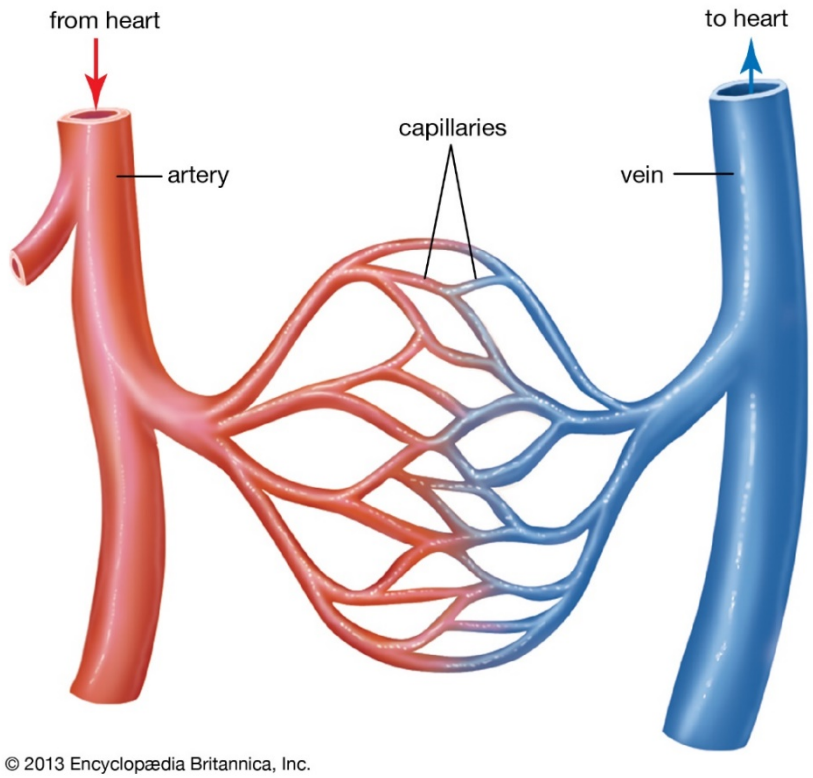

Figure 25: Capillaries

c. Veins

Veins carry blood toward the heart. After blood passes through the capillaries, it enters the smallest veins, called venules. From the venules, it flows into progressively larger and larger veins until it reaches the heart. In the pulmonary circuit, the pulmonary veins transport blood from the lungs to the left atrium of the heart. This blood has a high oxygen content because it has just been oxygenated in the lungs. Systemic veins transport blood from the body tissue to the right atrium of the heart. This blood has a reduced oxygen content because the oxygen has been used for metabolic activities in the tissue cells.

The walls of veins have the same three layers as the arteries. Although all the layers are present, there is less smooth muscle and connective tissue. This makes the walls of veins thinner than those of arteries, which is related to the fact that blood in the veins has less pressure than in the arteries.

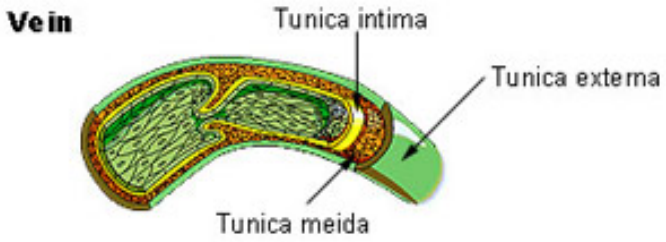

Figure 26: Structure of a vein

Because the walls of the veins are thinner and less rigid than arteries, veins can hold more blood. Almost 70 percent of the total blood volume is in the veins at any given time. Medium and large veins have venous valves, similar to the semilunar valves associated with the heart, that help keep the blood flowing toward the heart. Venous valves are especially important in the arms and legs, where they prevent the backflow of blood in response to the pull of gravity.

II. Cardiovascular diseases

The field of cardiology has come a long way since John Warren published his "Remarks on Angina Pectoris" in the first issue of the *New England Journal of Medicine* in 1812. Although his description of angina pectoris still resonates today, our understanding and treatment of cardiovascular disease has changed drastically.

Cardiovascular disease is any of the diseases, whether congenital or acquired, of the heart and blood vessels. Among the most important are atherosclerosis, rheumatic heart disease, and vascular inflammation. The risk of certain cardiovascular diseases may be increased by smoking, high blood pressure, high cholesterol, unhealthy diet, lack of exercise, and obesity. Cardiovascular diseases are a major cause of health problems and death.

1. Congenital heart disease

The heart's complicated evolution during embryological development presents the opportunity for many different types of congenital defects to occur. Congenital heart disease is one of the important types of diseases affecting the cardiovascular system. Most patients the causes appear to fit in the middle of a continuum from primarily genetic to primarily environmental.

Of the few cases that have a genetic nature, the defect may be the result of a single mutant gene, while in other cases it may be associated with a chromosomal abnormality, the most common of which is Down syndrome, in which about 50 percent of afflicted children have a congenital cardiac abnormality. In the even smaller number of cases of an obvious environmental cause, a variety of specific factors are evident. The occurrence of rubella (German measles) in a woman during the first three months of pregnancy is caused by a virus and is associated in the child with patent ductus arteriosus (nonclosure of the opening between the aorta and the pulmonary artery). Other viruses may be responsible for specific heart lesions, and a number of

drugs, including antiepileptic agents, are associated with an increased incidence of congenital heart disease.

Congenital cardiac disturbances are varied and may involve almost all components of the heart and great arteries. Some may cause death at the time of birth, others may not have an effect until early adulthood, and some may be associated with an essentially normal life span. Nonetheless, about 40 percent of all untreated infants born with congenital heart disease die before the end of their first year.

Congenital heart defects can be classified into cyanotic and noncyanotic varieties. In the cyanotic varieties, a shunt bypasses the lungs and delivers venous (deoxygenated) blood from the right side of the heart into the arterial circulation. The infant's nail beds and lips have a blue color due to the excess deoxygenated blood in the system. Some infants with severe noncyanotic varieties of congenital heart disease may fail to thrive and may have breathing difficulties

2. Acquired heart disease

Acquired heart diseases are defined as the conditions affecting the heart and its associated blood vessels that develop during a person's lifetime, in contrast to congenital heart diseases, which are present at birth. Acquired heart diseases include coronary artery disease, coronary heart disease, rheumatic heart disease, diseases of the pulmonary vessels and the aorta, diseases of the tissues of the heart, and diseases of the heart valves, arrhythmia, myocarditis, cardiomyopathy, heart failure, hypertension, syncope, and so on. In medicine, more and more attention is paid to those diseases since they impact the quality of life greatly. The burden of illness associated with an acquired cardiac disease is significant and may be equivalent to that of congenital heart disease. Moreover, the treatment and its outcomes may be utterly different for children than for adults with the same acquired heart disease because of the unique developing characteristics in children.

3. High blood pressure

High blood pressure (HBP), cigarette smoking, diabetes mellitus (DM), and lipid abnormalities are major modifiable risk factors for cardiovascular disease (CVD). Among these, high BP is associated with the strongest evidence for causation and has a high prevalence of exposure. However, there is considerable evidence that a biologically normal level of BP in humans is considerably lower than what has been traditionally employed in clinical practice and research, leading to an underrepresentation of the role that BP plays as a risk factor for CVD. The following integrated theory was proposed for CVD causation that is supported by a robust body of coherent and consistent evidence: CVD in humans is primarily caused by a right-sided shift in the distribution of BP.

III. Relationship between cardiovascular diseases and ABO blood group system

A study done in Wuxi School of Medicine, Jiangnan University, China. Written by Xiaofeng Dai, entitled by "**ABO blood group predisposes to COVID-19 severity and cardiovascular"** diseases says that one important epidemiological clinical characteristic of COVID-19 is the enrichment of severe patients with cardiovascular disease carriers especially hypertension. Hypertensive patients typically have over-elevated ACE/ANGII axis, in which ACE positively regulates the level of angiotensin II (ANGII) in the renin–angiotensin–aldosterone system (RAS). Drugs that inhibit the RAS, namely ACE inhibitors and angiotensin receptor antagonists (ARAs), are common medications for hypertension management. While ACE is hypertension promoting, ACE2 counterbalances the effects of ACE and delivers many beneficial effects to human health including attenuating inflammatory response and redox stress. It was reported that the ABO blood group is associated with ACE activity and ACE inhibitor-induced cough among Chinese patients with essential hypertension. That is, the GATC haplotype of the four polymorphisms of the ABO gene, which is prevalent among non-O blood type patients, is positively associated with ACE activity. Thereby, **O blood type carriers should have lower ACE levels** and **a higher probability of enjoying protection from ACE2-conveyed benefits. Consistent with this, blood type O carriers have a higher interleukin 6 (IL-6) level** than non-type O carriers. IL-6 is a proinflammatory cytokine triggering the production of acute-phase proteins such as C-reactive protein. As higher levels of C-reactive protein were detected among ACE-inhibitor-induced coughers than controls, a positive relationship between IL-6 secretion and ACE inhibitor and/or ACE2 is expected. A genome-wide association study (GWAS) found that blood type O carriers have increased IL-6 levels than individuals carrying the other blood group types, suggesting the advantages of blood type O over the other types in maintaining the dominant role of ACE2 in the RAS and thus a reduced risk of developing hypertension. On the contrary, the **A allele** of the ABO blood group has been associated with an **increased risk of developing cardiovascular** diseases as reported by several studies. The A antigen might protect P-selectin and intercellular cell adhesion molecule 1 (ICAM1) from enzymatic cleavage by promoting stronger and longer binding of leukocytes to them on the vascular wall; more adhesion molecules attached to the endothelial cells would on one hand increase adhesion and inflammation but on the other hand decrease circulation. These collectively predispose type A carriers to a higher likelihood of developing cardiovascular diseases and aggregate disease situations once these individuals were exposed to redox stresses such as in the case of virus infection. Therefore, individuals having an **O blood group type are less likely to develop cardiovascular diseases** and severe COVID-19 and, on the contrary, patients carrying an **A blood group type**, especially those already having been diagnosed with cardiovascular diseases in particular hypertension, are **more likely to develop severe COVID-19 once infected**.

Practical part

Chapter 4: Materials and methods

I. Materials

1. The human sample

A number of samples was collected, which is estimated to be one thousand and ninety-two samples (1092) in the whole Wilaya of Khenchela.

The collected sample is referred to the month of June, 2021 and July from 2021 as well. It was gathered by demanding from doctors from different hospital institutions and clinics to fill a form in which the blood group type, age, sex, disease and region are provided.

The number is divided by several regions, The table below in the next chapter shows the exact results.

2. Informatic material

The software used to analyse data: Statistica six sigma, 7th edition. In addition to Office Excel 2019.

The laptop: hp Intel Core i7, 2nd generation, RAM of 8 GB and a x64 based processor.

II. Methods

The methods used in this study are purely statistical.

To determine the existence of correlation between the blood group system of the collected sample and the type of cardiovascular disease they have, the correlation analysis was conducted by using Statistica software.

To be more precise; we depended on Principal Component Analysis (PCA).

PCA is an unsupervised statistical technique algorithm. PCA is a “dimensionality reduction” method. It reduces the number of variables that are correlated to each other into fewer independent variables without losing the essence of these variables or any important information. It provides an overview of linear relationships between inputs and variables.

The main idea behind PCA is to figure out patterns and correlations among various features in the dataset. On finding a strong correlation between different variables, a final decision is made about reducing the dimensions of the data in such a way that the significant data is still retained. Such a process is very essential in solving complex data-driven problems that involve the use of high-dimensional data sets.

Table 3: Clear dataset gathering blood group types and cardiopathies they are related to

	Arrhythmia	HBP	Hyperlipidemia	Ischemic cardiomyopathy	Congenital cardiopathy	Myocardiopathy	Peripherical artery
A+	92	392	13	56	4	3	0
A-	1	5	1	1	0	0	0
B+	15	55	1	7	1	0	0
B-	0	2	0	0	0	0	0
AB+	5	9	0	1	0	0	0
AB-	0	1	0	0	0	0	0
O+	65	248	8	21	0	1	1
O-	16	59	1	4	0	0	0

To perform dimensionality reduction using PCA, a few steps need to be followed:

a. Standardization of the data

Missing out on standardization will probably result in a biased outcome. Standardization is all about scaling data in such a way that all the variables and their values lie within a similar range.

It can be calculated by:

$$Z = \frac{X - \bar{X}}{SD}$$

Knowing that X is the variable value, $\bar{X}$ is the mean and SD is the standard deviation.

b. Computing the Covariance Matrix

A covariance matrix expresses the correlation between the different variables in the data set. It is essential to identify heavily dependent variables because they contain biased and redundant information which reduces the overall performance of the model.

Mathematically, a covariance matrix is a p × p matrix, where p represents the dimensions of the data set. Each entry in the matrix represents the covariance of the corresponding variables. In our case, we have a 7-Dimensional data set with variables a, b, c, d, e, f and g named respectfully: Arrhythmia, HBP, Hyperlipidemia, Ischemic cardiomyopathy, Congenital cardiopathy, Myocardiopathy and Peripherical artery. the covariance matrix is a 7×7 matrix as shown below:

Cov (a, a)	Cov (b, a)	Cov (c,a)	Cov (d, a)	Cov (e, a)	Cov (f, a)	Cov (g, a)
Cov (a, b)	Cov (b, b)	Cov (c,b)	Cov (d, b)	Cov (e, b)	Cov (f, b)	Cov (g, b)
Cov (a, c)	Cov (b, c)	Cov (c,c)	Cov (d, c)	Cov (e, c)	Cov (f, c)	Cov (g, c)
Cov (a, d)	Cov (b, d)	Cov (c,d)	Cov (d, d)	Cov (e, d)	Cov (f, d)	Cov (g, d)
Cov (a, e)	Cov (b, e)	Cov (c,e)	Cov (d, e)	Cov (e, e)	Cov (f, e)	Cov (g, a)
Cov (a, f)	Cov (b, f)	Cov (c,f)	Cov (d, f)	Cov (e, f)	Cov (f, f)	Cov (g, a)
Cov (a, g)	Cov (b, g)	Cov (c,g)	Cov (d, g)	Cov (e, g)	Cov (f, g)	Cov (g, a)

- The covariance value denotes how co-dependent two variables are with respect to each other.
- If the covariance value is negative, it denotes the respective variables are indirectly proportional to each other.
- A positive covariance denotes that the respective variables are directly proportional to each other.

c. Calculating the Eigenvectors and Eigenvalues

Eigenvectors and eigenvalues are the mathematical constructs that must be computed from the covariance matrix in order to determine the principal components of the data set. And a principal component is the new set of variables that are obtained from the initial set of variables. The data set is of 7 dimensions, then 7 principal components are computed, such that, the first principal component stores the maximum possible information, and the second one stores the remaining maximum info and so on.

The idea behind eigenvectors is to use the Covariance matrix to understand where in the data there is the most amount of variance (since more variance in the data denotes more information about the data) eigenvectors and eigenvalues are used to identify and compute principal components.

d. Computing the Principal Components

Once the eigenvectors and eigenvalues are computed, they have to be ordered them in the descending order, where the eigenvector with the highest eigenvalue is the most significant and thus forms the first principal component. The principal components of lesser significances can thus be removed in order to reduce the dimensions of the data. The final step in computing the Principal Components is to form a matrix known as the feature matrix that contains all the significant data variables that possess maximum information about the data.

Usually, having a good amount of data lets us build a better predictive model since we have more data to train the machine with. Unfortunately, our sample is not large enough, the number “1092” does not really allow researchers and studies builders to reach reliable results, nevertheless, the results we reached were harmonious and compatible with what science has concluded.

Chapter 5: Results and discussion

In this chapter we will present the results found in details.

1. Results

a. ABO blood groups distribution

Table 4: Count of ABO blood groups

Blood group	Count of Blood group
A-	8
A+	560
AB-	1
AB+	15
B-	2
B+	79
O-	82
O?	1
O+	342
Rh +	1

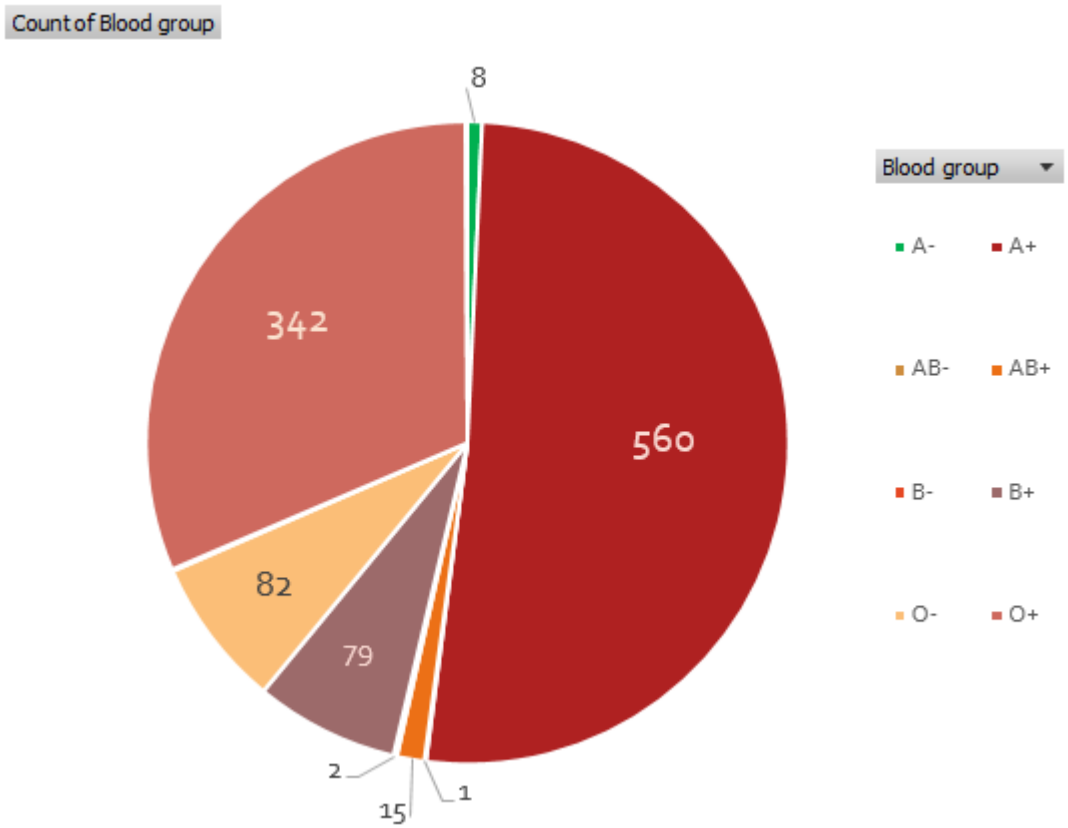

Figure 27: Count of blood groups

b. Count of disease

Table 5: Count of cardiopathies found in Khenchela province

Disease	Count of Disease
Arrhythmia	195
Cogenital cardiopathy	5
HBP	772
Hyperlipidemia	24
Ischemic cardiomyopathy	90
myocardiopathie	3
Myocardiopathy	1
Peripheral artery	1

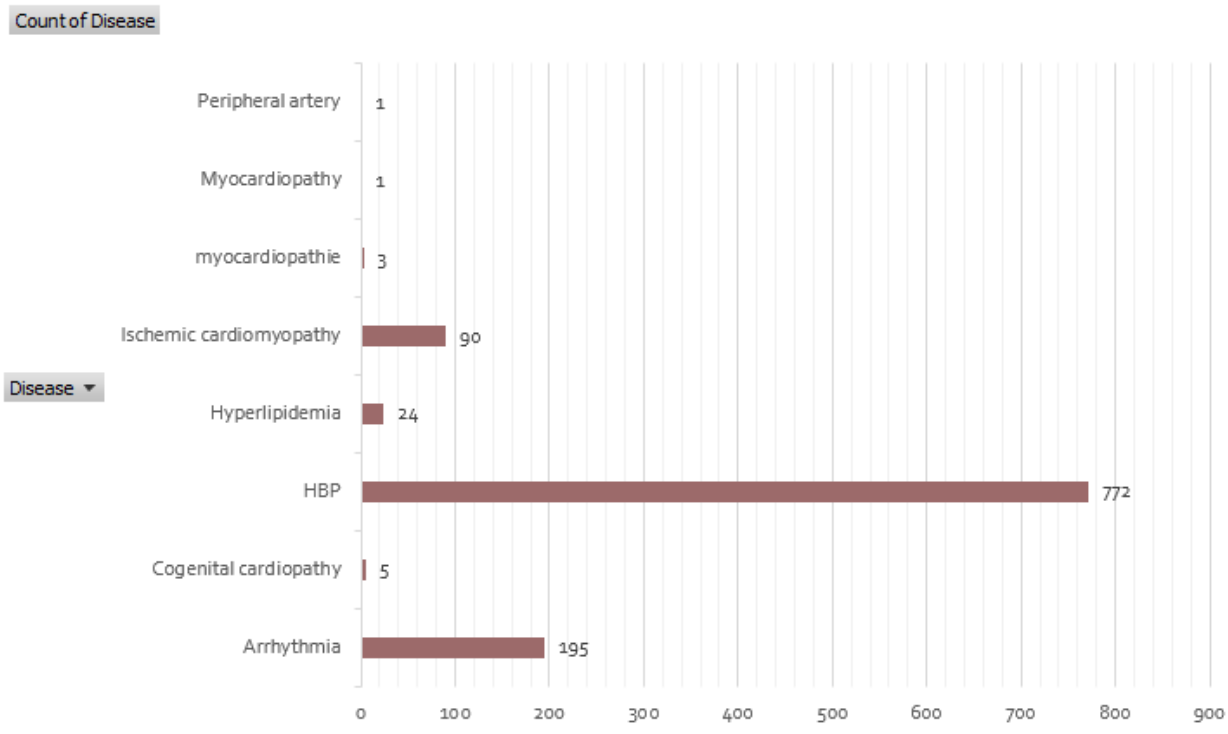

Figure 28: Count of disease found in Khenchela province

c. Count of age

The age in the sample is between 28 days and 92 years old; we can observe that cardiopathies are more common among people who are between forties and eighties.

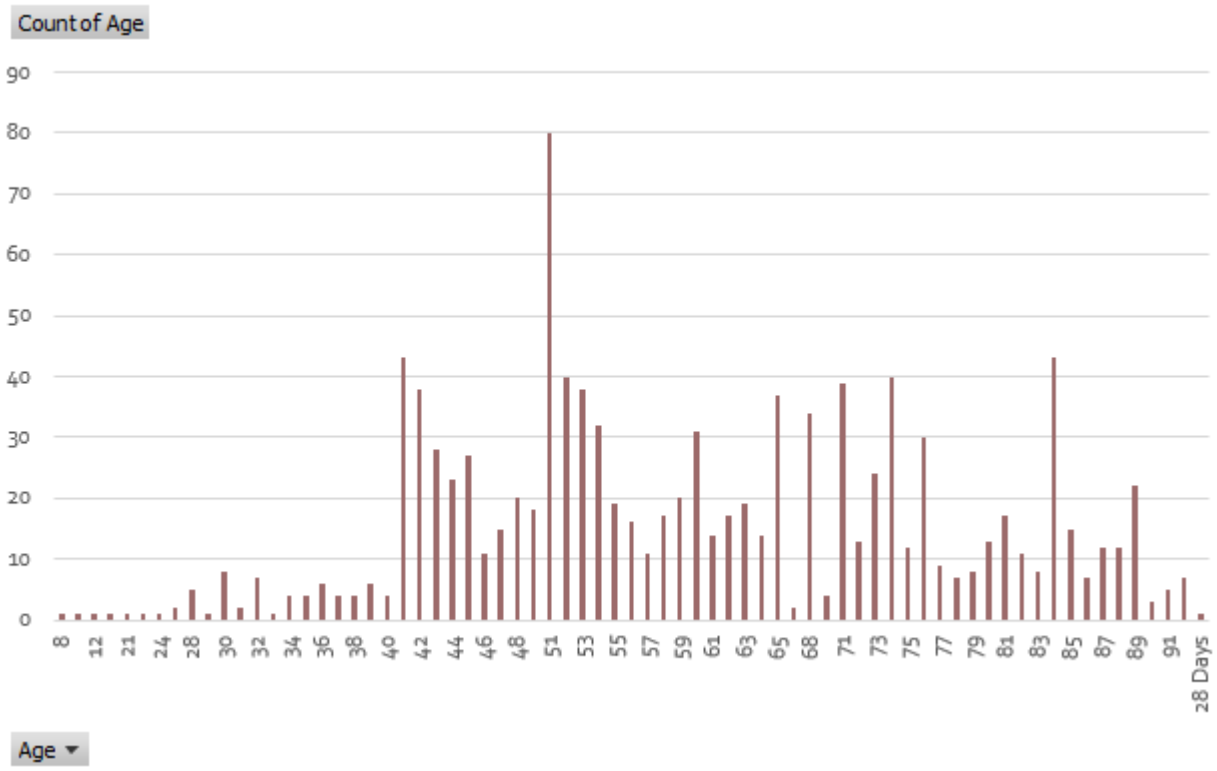

Figure 29: Count of age in the study sample

d. Count of sex

The number of females in this sample is 31.6% more than males number.

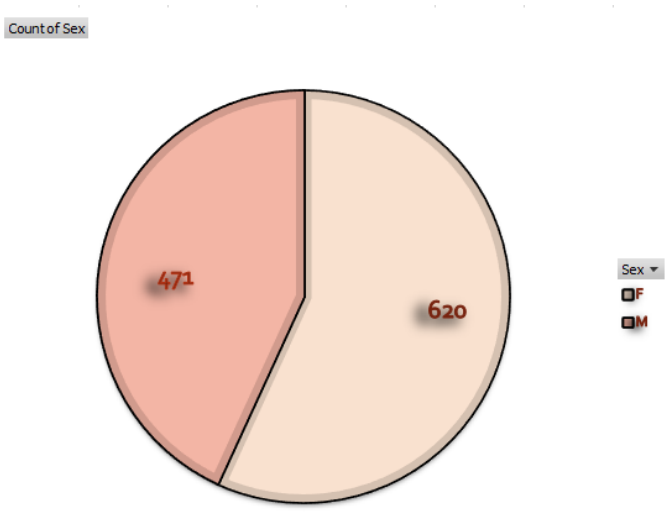

Figure 30: Count of sex in the sample

e. Count of sample divided by regions

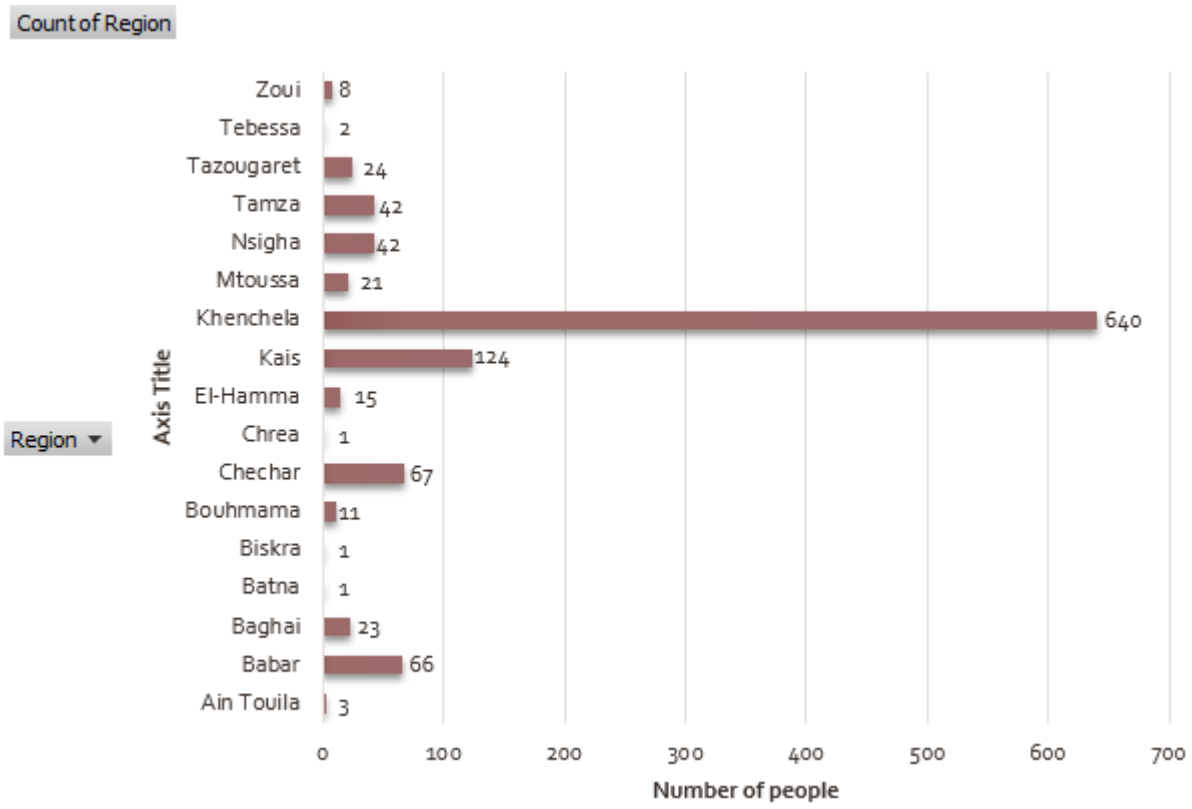

Figure 31: Count of people divided by regions of Khenchela province

Table 6: Count of sample divided by regions in Khenchela province

Region	Count of region
Ain Touila	3
Babar	66
Baghai	23
Batna	1
Biskra	1
Bouhmama	11
Chechar	67
Chrea	1
El-Hamma	15

Kais	124
Khenchela	640
Mtoussa	21
Nsigha	42
Tamza	42
Tazougaret	24
Tebessa	2
Zoui	8

Data conducted by Statistica software

a. Count of cardiopathies with each blood group in both ABO and Rh systems

Table 7: Count of diseases with each blood group type

	Arrhythmia	HBP	Hyperlipidemia	Ischemic cardiomyopathy	Congenital cardiopathy	Myocardiopathy	Peripherical artery
A+	92	392	13	56	4	3	0
A-	1	5	1	1	0	0	0
B+	15	55	1	7	1	0	0
B-	0	2	0	0	0	0	0
AB+	5	9	0	1	0	0	0
AB-	0	1	0	0	0	0	0
O+	65	248	8	21	0	1	1
O-	16	59	1	4	0	0	0

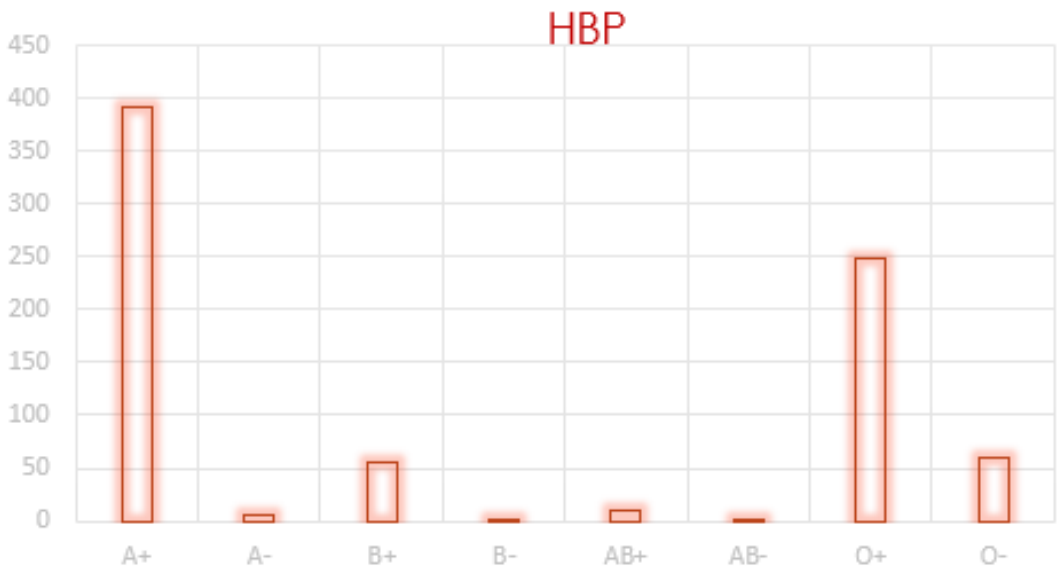

Figure 33: Count of ABO & Rh blood groups in HBP patients sample

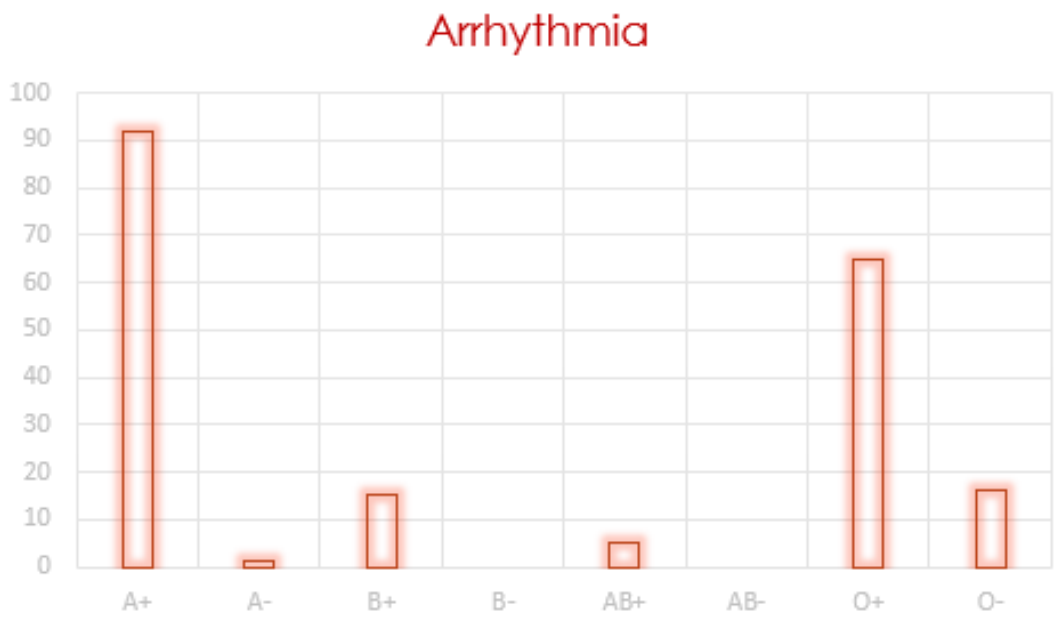

Figure 32: Count of ABO & Rh blood groups in Arrhythmia patients sample

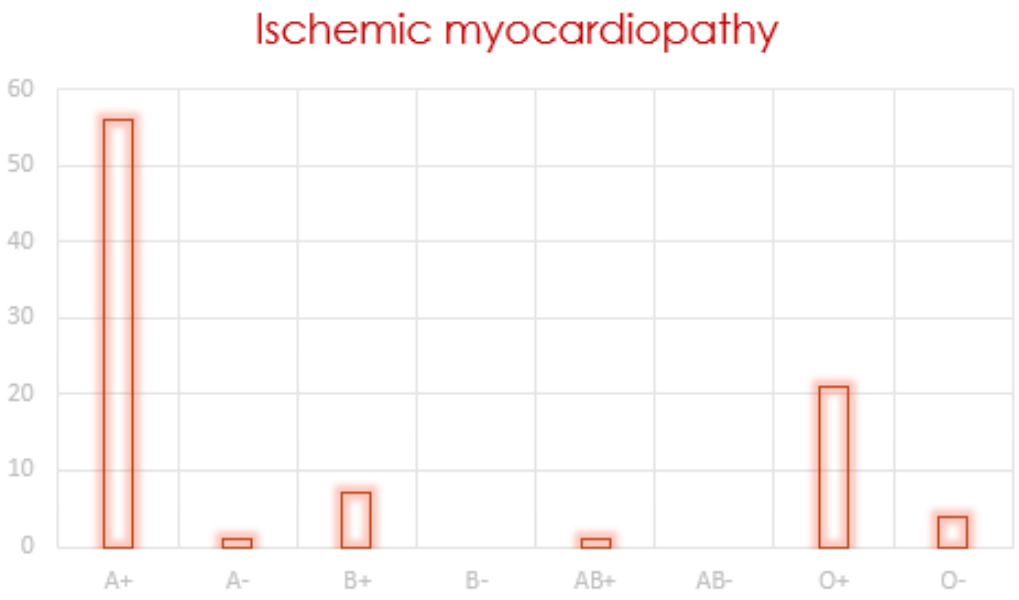

Figure 35: Count of ABO & Rh blood groups in Ischemic myocardiopathis patients sample

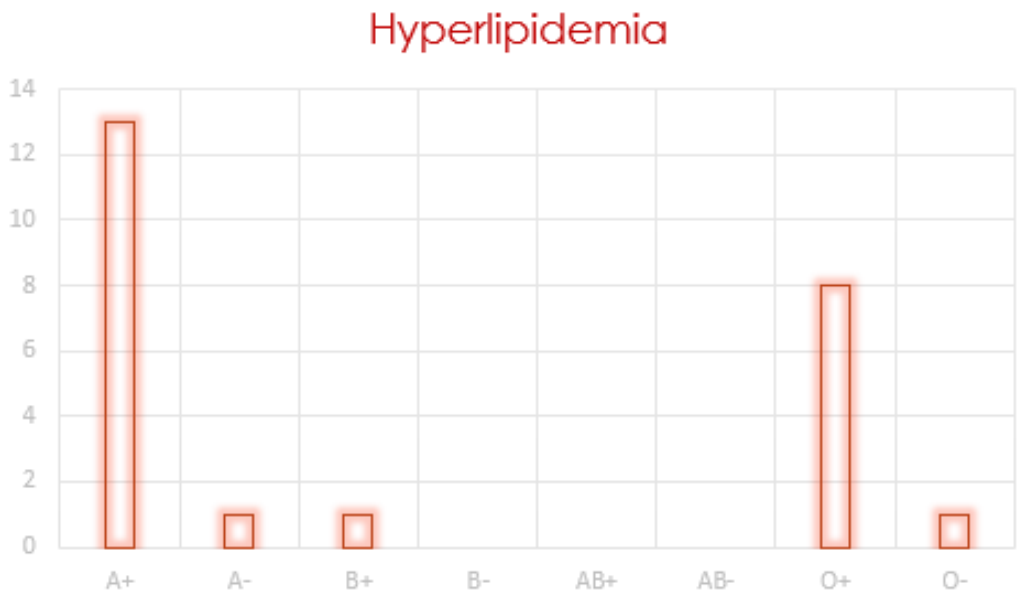

Figure 34: Count of ABO & Rh blood groups in Hyperlipidemia patients sample

b. Factor coordinates of the variables, based on correlations

Table 8: Factor coordinates of the variables, based on correlations

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Arrhythmia	0.982454	0.166627	-0.039514	0.072319	0.011792	0.009389
HBP	0.992115	0.109592	-0.018869	0.056261	0.002022	-0.013108
Hyperlipidemia	0.991878	0.103875	0.053570	-0.014564	-0.047990	0.001556
Ischemic cardiomyopathy	0.992167	-0.124826	0.002613	0.000777	0.002133	0.003414
Congenital cardiopathy	0.860007	-0.493552	-0.113087	-0.063278	0.000175	-0.000674
Myocardiopathy	0.983007	-0.134852	0.113715	-0.041163	0.029789	-0.000490
Peripherical artery	0.323645	0.943638	-0.039280	-0.056577	0.007597	-0.000278

c. Factor coordinates of cases, based on correlations

Table 9: Factor coordinates of cases, based on correlations

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
A+	5.22972	-1.23056	0.056588	-0.007410	0.003965	-0.000016
A-	-1.32477	-0.18899	0.143230	-0.081178	-0.122512	0.009802
B+	-0.63348	-0.44670	-0.425896	-0.052872	-0.015760	-0.000044
B-	-1.45212	-0.20898	0.089178	-0.083222	0.039211	-0.020131
AB+	-1.35182	-0.18836	0.053166	0.016050	0.071821	0.033664
AB-	-1.45498	-0.20967	0.089905	-0.086151	0.038971	-0.014684
O+	1.91707	2.57780	-0.017405	-0.018527	0.001096	-0.000011
O-	-0.92963	-0.10454	0.011233	0.313310	-0.016792	-0.008578

d. Projection of the cases on factor-plane

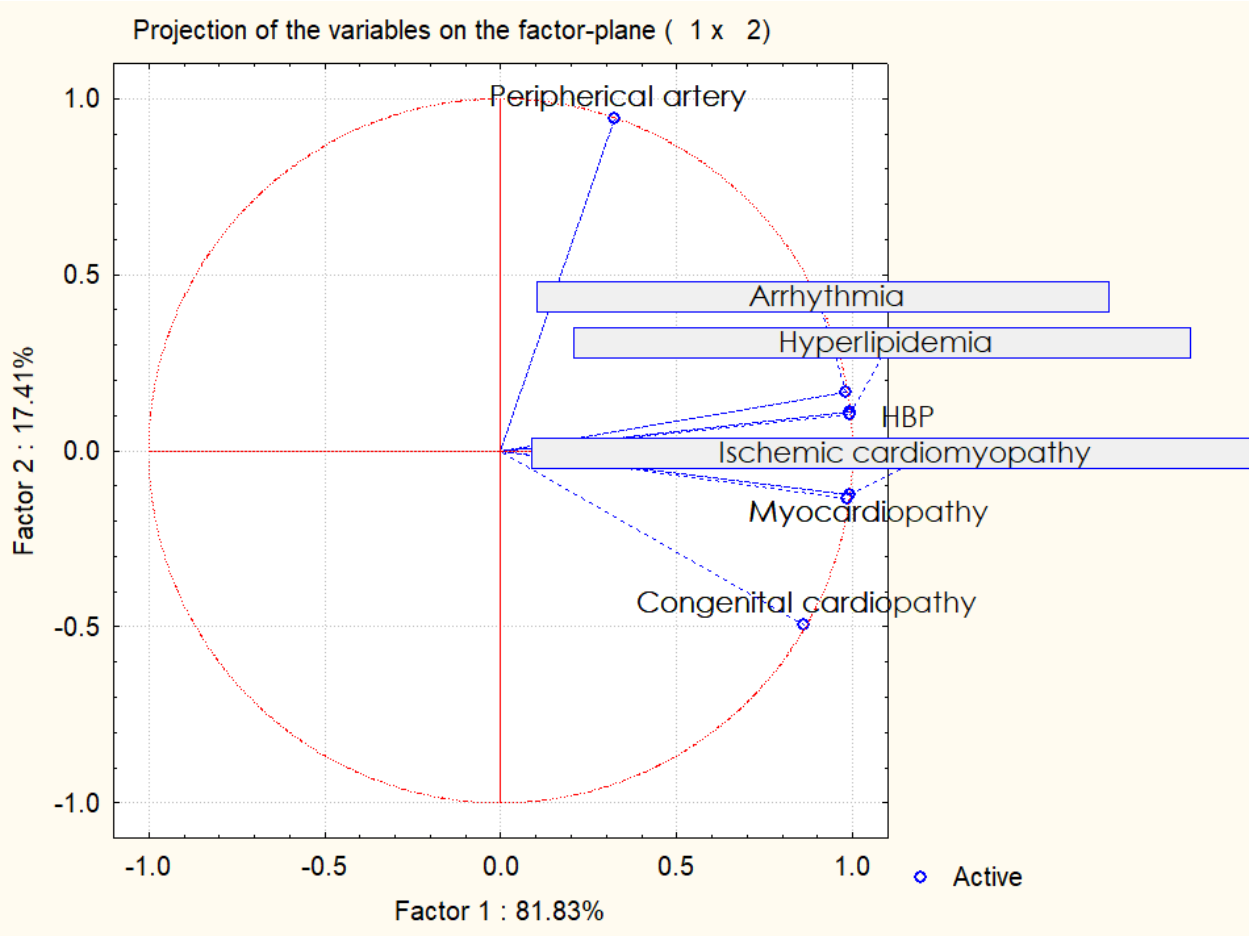

Figure 36: Projection of the cases on factor-plane

e. Eigenvalues of correlation matrix

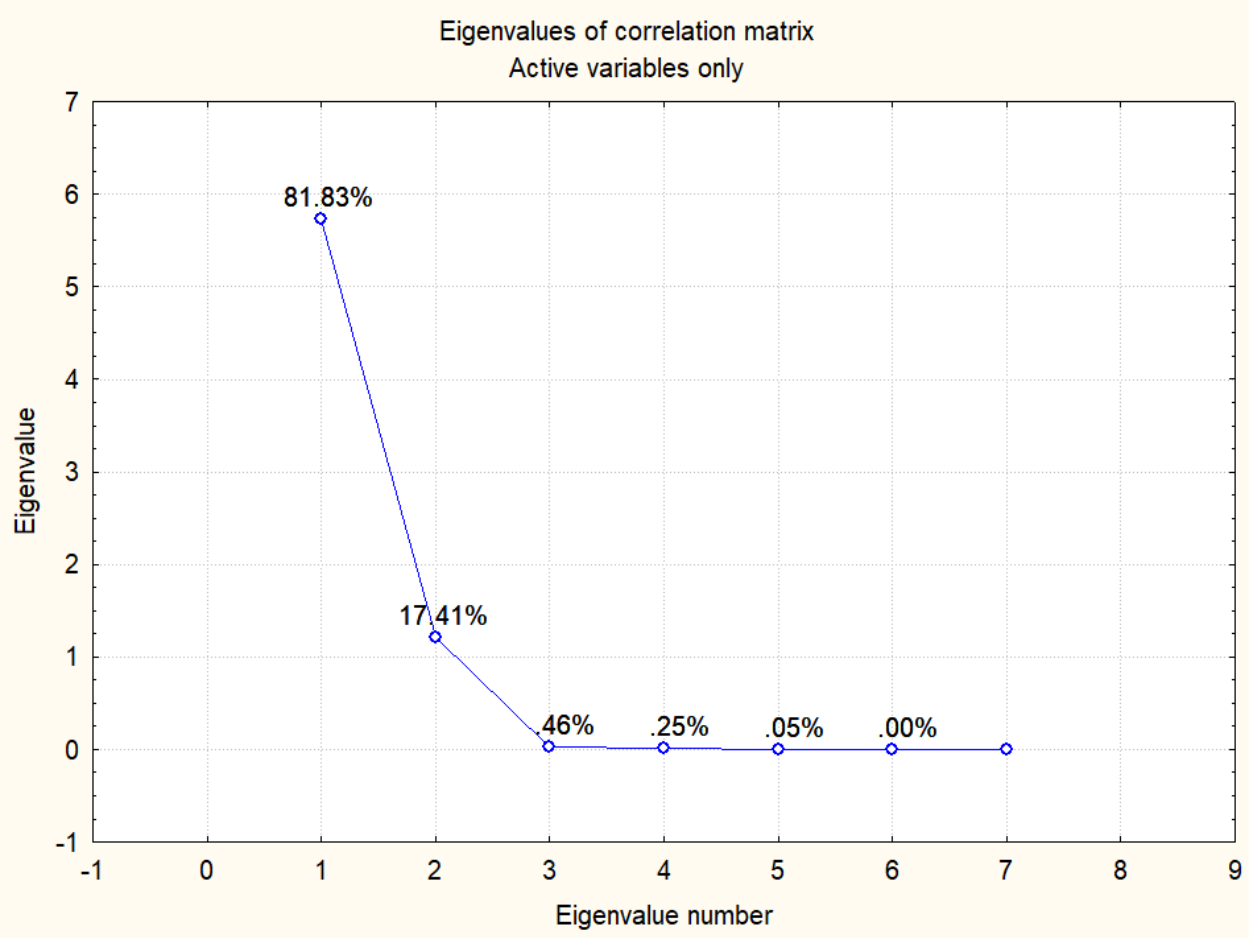

Figure 37: Eigenvalues of correlation matrix

f. Factor-variable correlations (factor loadings), based on correlations

Table 10: Factor-variable correlations (factor loadings), based on correlations

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Arrhythmia	0.982454	0.166627	-0.039514	0.072319	0.011792	0.009389
HBP	0.992115	0.109592	-0.018869	0.056261	0.002022	-0.013108
Hyperlipidemia	0.991878	0.103875	0.053570	-0.014564	-0.047990	0.001556
Ischemic	0.992167	-0.124826	0.002613	0.000777	0.002133	0.003414

cardiomyopathy						
Congenital cardiopathy	0.860007	-0.493552	-0.113087	-0.063278	0.000175	-0.000674
Myocardiopathy	0.983007	-0.134852	0.113715	-0.041163	0.029789	-0.000490
Peripherical artery	0.323645	0.943638	-0.039280	-0.056577	0.007597	-0.000278

g. Factor scores, based on correlations

Table 11: Factor scores, based on correlations

	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**	**Factor 6**
A+	2.185055	-1.11484	0.31606	-0.056005	0.06804	-0.00099
A-	-0.553508	-0.17122	0.79998	-0.613514	-2.10235	0.59125
B+	-0.264675	-0.40469	-2.37873	-0.399592	-0.27044	-0.00267
B-	-0.606718	-0.18933	0.49808	-0.628965	0.67286	-1.21434
AB+	-0.564811	-0.17065	0.29694	0.121304	1.23247	2.03064
AB-	-0.607911	-0.18995	0.50214	-0.651104	0.66876	-0.88574
O+	0.800981	2.33538	-0.09721	-0.140020	0.01880	-0.00069
O-	-0.388413	-0.09471	0.06274	2.367897	-0.28815	-0.51746

h. Correlations between Cardiopathies

Table 12: Correlations between cardiopathies of the sample

	Arrhythmia	HBP	Hyper-lipidemia	Ischemic cardiomyo-pathy	Congenital cardiopathy	Myocardio pathy	Peripherical artery
Arrhythmia	1.000000	0.997684	0.988063	0.953970	0.762567	0.936165	0.472750
HBP	0.997684	1.000000	0.993494	0.970618	0.797720	0.956082	0.422085
Hyper-lipidemia	0.988063	0.993494	1.000000	0.971174	0.796609	0.966276	0.417392
Ischemic cardio-myopathy	0.953970	0.970618	0.971174	1.000000	0.914532	0.992466	0.203188
Congenital cardiopathy	0.762567	0.797720	0.796609	0.914532	1.000000	0.901700	-0.179374
Myocardio-pathy	0.936165	0.956082	0.966276	0.992466	0.901700	1.000000	0.188982
Peripherical artery	0.472750	0.422085	0.417392	0.203188	-0.179374	0.188982	1.000000

2. Discussion

Table 4 represents the count of ABO blood groups; as we observe that the A+ blood group is the most common among this sample of citizens. It represents 50.28% from total blood groups. The O+ blood group represents 342 from 1092 or 29.67%. which means the rest of the blood groups represent only 19.05% in this sample.

Figure 28 and **Table 5** represent the count of cardiopathies found in different regions of Khenchela province. It is remarkable that the factor of High Blood Pressure is the most prevalent (772 patient or 70.69%), next comes Arrhythmia with the count of 195 patients (17.85%). Ischemic cardiomyopathies represent 8.24% from the total number of patients.

Figure 29 shows that the interval [41,84] years old is when people are more susceptible to get one of the mentioned heart issues, with the highest possibilities to the first fifties.

Figure 30: The number of females in this sample is 31.6% more than males number. Female patients represent 56.77% (620), where males represent 43.13% (471).

Figure 31 and **Table 6** both represent the count of patients in different regions of Khenchela province; Khenchela region itself has gotten the biggest share with 640 patients (58.60%), Kais region comes second with the number of 124 patients or 11.35%, Chechar and Babar region are almost equal with 6.1% each. This is explained by the fact that the data set was gathered from Khenchela region hospitals and clinics.

When The data set was merged and cleaned, **Table 7** was created. It represents the count of diseases with each blood group (ABO & Rh blood group systems). HBP is the most widespread heart issue as mentioned earlier. A+ and O+ blood groups are _again_ the most common too.

Table 8 represents the factor coordinates of the variables, based on correlations. It is recommended to consider the two first factors, for they have the highest values.

The correlation coefficient is measured on a scale that varies from + 1 through 0 to – 1. Complete correlation between two variables is expressed by either + 1 or -1. When one variable increases as the other increases the correlation is positive; when one decreases as the other increases it is negative. Complete absence of correlation is represented by 0.

As can be seen in the table, there is no perfect positive or negative correlation (the highest value is 0.992167; between Hyperlipidemia and Factor 1. And the lowest value is -0.000674; between Congenital cardiopathy and Factor 6. There is also no absence of correlation (value 0).

Between Factor 1 and:

- Arrhythmia, HBP, Hyperlipidemia, Ischemic cardiomyopathy and Myocardiopathy have very high positive correlation ([+0.90 to +0.99]).
- Congenital cardiopathy there exists a high positive correlation (+0.86 Є [+0.70 to +0.90]).
- Peripherical artery there is a low positive correlation (+0.32 Є [+0.30 to +0.50]).

Between Factor 2 and:

- Peripherical artery, the correlation is very high positive (+0.94 Є [+0.90 to +0.99]).
- Arrhythmia, HBP and Hyperlipidemia there is very low positive correlation ([+0.10 to +0.30]).
- Ischemic cardiomyopathy and Myocardiopathy is very low negative correlation ([-0.10 to -0.30]).
- Congenital cardiopathy, we observe a low negative correlation (-0.49 Є [-0.30 to -0.50]).

Table 9: represents factor coordinates of cases, based on correlations; A+ and O+ are both > 1 with Factor 1, whereas other blood types coefficients are between 1 and -2. This can be explained by the great number of patients that carry those two blood types comparing to other patients with different blood types, the data set is non-homogeneous.

And for Factor 2; only O+ has a very high positive correlation.

We can anticipate from **Figure 32** the seriousness among 7 different types of cardiovascular diseases.

The factor coordinates of the variables are the correlations of the variables and the factor axes In a 2D graphical representation, they fall in a circle, called the correlation circle (figure 32) with the pair of factor axes as its axes. The variables, when projected onto this circle, reveal a lot about themselves. For instance, the further a point is from the origin of the circle, the greater the correlation of the corresponding variable with the factor axes. In this case, all 7 variables distance is equal to 1.

Similarly, the position of the factor coordinate of a variable with respect to the factor axes classifies it into one or the other category. For example, starting with the first factor axis, the variables can be classified into two categories, depending upon which side of the factor axis the corresponding factor coordinates of the variables lie. In other words, the classification of variables is done according to the sign of the factor coordinates.

Factor 1 is 81.83% depended on, while Factor 2 is only 17.41% depended on.

Table 12: This table represents the correlations between cardiopathies of the sample we are working on; and how likely a person can get two or more diseases at the same time.

We can observe that the coefficient 1 can only be given when the disease with itself. However, there are diseases that present a very high or high positive correlation, which means there is a high possibility that a person can get them at the same time:

- Arrhythmia with: HBP, Hyperlipidemia and Ischemic cardiomyopathy present a very high positive correlation: 0.99, 0.98 and 0.95 respectively
- Arrhythmia and Congenital cardiomyopathy present a high positive correlation as well: 0.76
- Arrhythmia and Peripherical artery present a low positive correlation: 0.47
- HBP with Hyperlipidemia, Ischemic and Myocardiopathy present a very high positive correlation: 0.99, 0.97 and 0.95 respectively
- HBP with Congenital cardiopathy present high positive correlation: 0.79
- HBP with Peripherical artery present low positive correlation: 0.42
- Hyperlipidemia with Ischemic cardiomyopathy and Myocardiopathy present very high positive correlation: 0.97 and 0.96 respectively
- Hyperlipidemia with Congenital cardiopathy present high positive correlation: 0.79
- Hyperlipidemia with Peripherical artery present low positive correlation: 0.41
- Ischemic cardiomyopathy presents very high positive correlation with both Congenital cardiopathy and Myocardiopathy: 0.91 and 0.99 respectively, and it presents low positive correlation with peripherical artery
- Congenital cardiopathy presents very high positive correlation with Myocardiopathy (0.90), but very low negative correlation with Peripherical artery (-0.17)
- Last, Myocardiopathy presents very low positive correlation with Peripherical artery

We deduce from this interpretation that: the higher the correlation is, the bigger the possibility that one can get those diseases together, at the same time. In other words; the diseases are accompanied.

Conclusion

CONCLUSION

General conclusion

The ABO blood groups have a profound influence on human bodies overall health. For instance; on haemostasis. They exert major quantitative effects on plasma levels of von Willebrand factor and factor VIII. Increased association of myocardial infarction, ischemic stroke, and venous thromboembolism is seen with blood groups A and AB possibly through functional ABO glycol transferases modulation of thrombosis. A higher risk of cerebral venous thrombosis has been reported in non-O groups. Significant association of ABO groups with the prevalence of preeclampsia has been reported, where AB group was found to be associated with an increased risk of 2.1-folds. Preliminary studies suggested an association of ABO system with malignancies. A positive correlation has been shown between blood group A with chronic hepatitis-B infection and pancreatic cancer; and blood group B with ovarian cancer. Protection against falciparum malaria can be achieved with group O by reducing rosette formation. Blood group O increases the severity of infection in Vibrio cholerae strains.

This study in Khenchela province has concluded that the ABO & Rh blood group systems do have substantial effect on the heart well-being. Significantly higher possibilities of getting one of the cardiovascular diseases were observed with A+, and O+ blood groups respectively.

It is a common error to confuse correlation and causation. If two variables are correlated, they are not necessarily causally related. All that correlation shows is that the two variables are associated (Blood group and disease). There may be a third variable, a confounding variable that is related to both of them. Correlation does not imply causation.

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Abstract

This study aims to investigate the relationship of blood group systems ABO & Rh (A+, A-, B+, B-, AB+, AB-, O+, O-) with cardiovascular disease, specifically: high blood pressure (HBP), Arrhythmia, Hyperlipidemia, Ischemic cardiomyopathy, Congenital cardiopathy, Myocardiopathy and Peripherical artery, n several regions in the wilaya of Khenchela. Using a statistical computer program; Statistica software, and analyzing the data obtained by Principal Compound Analysis (PCA).

Therefore, it was concluded that the blood group systems have a big linkage with cardiovascular diseases selected in this study, and that blood groups A+ and O+ are more susceptible to some diseases than other blood groups.

الملخص

تهدف هذه الدراسة إلى معرفة مدى ترابط أنظمة الزمر الدموية ABO وريزوس (A +، A-، B +، B-، AB +، AB-، O +، O-) بأمراض القلب والأوعية الدموية ، وتحديداً: ارتفاع ضغط الدم (HBP) ، عدم انتظام نبضات القلب، فرط الدهون في الدم، اعتلال عضلة القلب الإقفاري، اعتلال القلب الخِلقي، اعتلال عضلة القلب والشريان المحيطي، وهذا في عدة مناطق بولاية خنشلة. استُخدم برنامج حاسوب إحصائي؛ برنامج Statistica، لتحليل البيانات التي تم الحصول عليها وذلك بواسطة "تحليل المركب الرئيسي" (PCA).

وعليه، تم الخلوص إلى نتيجة مفادها أن لأنظمة الزمر الدموية ارتباط وثيق بأمراض القلب والأوعية الدموية المدروسة في هذه المذكرة، وأن فصائل الدم +A و+O هما الأكثر عرضة لبعض الأمراض من غيرهما من بقية فصائل الدم الأخرى.

Résumé

Cette étude vise à étudier la relation entre les systèmes de groupes sanguins ABO & Rh (A+, A-, B+, B-, AB+, AB-, O+, O-) avec les maladies cardiovasculaires, en particulier: l'Hypertension artérielle (HBP), l'Arythmie, l'Hyperlipidémie, l'Ischémie cardiomyopathie, Cardiopathie congénitale, Myocardiopathie et Artère périphérique, dans plusieurs régions de la wilaya de Khenchela. Utilisant un programme informatique statistique; logiciel Statistica, et en analysant les données obtenues par Composé principal analyse (CPA).

Par conséquent, il a été conclu que les systèmes de groupes sanguins ont un lien important avec les maladies cardiovasculaires sélectionnées dans cette étude, et que les groupes sanguins A+ et O+ sont plus sensibles à certaines maladies que d'autres groupes sanguins.