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RESEARCH ARTICLE

REVIEW OF PHYSIOLOGICAL FUNCTION OF *PITTADHARA KALA* W.S.R. TO ERYTHORPOIESIS

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ABSTRACT

Kala Sharir is an important part of *Ayurved* anatomy but not explained clearly in text. *Kala* is supposed to be situated between *Dhatu* and concerning *Ashaya*. It is formed with layers or membranes of our body and correlated with mucous, serous, fibrous membrane. There are many layers or membranes in the body which form an envelope over the organs. They provide support and protections to the organs. *Kala* are seven in number and *Pittadhara Kala* is sixth one present in between *Amashya* and *Pakwashaya* that is *Grahani* correlated as small intestine. *Pittadhara Kala* is correlated with the lining membranes of small intestine which plays vital role in digestion and absorption of all nutritive substances like Vit B12, Folic acid and iron which are the main factors for the process of formation and maturation of R.B.C. *Acharya Dalhan* had stated *Pittadhara Kala* as *Majjadhara Kala*. *Majja Dhatu* is present in the cavity of long bones which is correlated with bone marrow where R.B.C production takes place by Erythropoisis. Erythropoiesis is the process of the origin, development and maturation of erythrocytes. Impaired *Pittadhara Kala* causes malabsorption of Vit B12 and iron and leads to anemia.

INTRODUCTION

Ayurveda is the science which is based on various principles, one of them is *Kala* which is considered as an anatomical part only and remained neglected, where as *Kala* is having physiological and clinical relevance as well. *Kala* is defined as "*Dhatwashayantar Maryada*" which separates *Dhatu* (Tissue) and *Ashaya*. There are seven *Kala* explained in different *Samhita* among them *Pittadhara Kala* is sixth one situated between *Amashaya* (stomach) and *Pakwashaya* (large intestine) which is anatomical & physiological location for *Grahani* correlated with Small Intestine. *Grahani* (Small intestine) not only stores the *Chaturvidh-Ahara* (diet) but also promotes complete digesion, assimilation and absorption with help of *Pachaka Pitta* (digestive juice) which is produced by *Pittadhara Kala* with help of *Samana vayu*. Small intestine is the largest part of GIT present in between stomach and large intestine. It is major site for digestion and absorption of all nutrients like proteins, Vitamin B12, iron, folic acid, cobalt, manganese, calcium, proteins, nickel into the peripheral circulation. Location of *Majja Dhatu* is the cavity situated inside the long bones correlated as bone marrow. Erythropoiesis is the process of origination, formation and maturation of RBC which takes place in the bone marrow.

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A maturation factor which affects process of erythropoiesis are Vitamin B12, iron and folate which are absorbed from *Grahani* (small intestine) through *Pittadhara Kala* into the blood circulation, from there these factors are transported to the bone marrow correlated as *Majja Dhatu* to get utilized in the formation, maturation of RBC. During the stages of development and maturation of RBC i.e erythropoiesis, megaloblast are converted into primary erythroblast in presence of VitaminB12 and folate ,while primary erythroblast are converted into normoblast in presence of iron, copper, cobalt and other metals. Abnormality in the function of *Majja Dhatu* (bone marrow) leads to impaired RBCs production. Also alternation of physiological function of small intestine affects absorption of essential nutrients which plays as maturation factor in erythropoises which can lead to anaemia. *Acharya Dalhan* stated that *Pittadhara Kala* as *Majjadhara Kala* in *Sarpadashtavisha Adhyaya* in *Kalpasthana* of *Sushrut Samhita* because both the *Kala* plays vital role in RBC production. So this review study will help to analyze physiological function of *Pittadhara Kala* in process of formation and maturation of RBC W.S.R to erythopoiesis which can enlighten path for treating various hematological disorders related with R.B.C.

Aim

To study Physiological function of *Pittadhara Kala* W.S.R to Erythropoiesis.

Objective

1. To study concept of *Kala*
2. To study physiology of *Pittadhara Kala*.
3. To study role of *Pittadhara Kala* in absorption of influencing factors responsible for Erythropoiesis from small intestine
4. To study role of above factors in Erythropoiesis in bone marrow.
5. To study process of Ethrypoiesis.

Review of Literature

Kala: 'Dhatwashayanter Maryada' the one which separates Dhatu And Ashaya is defined as Kala[1]. The Ashaya is cavity which gives Ashraya to the Dosha, Dhatu and Mala [2]. Snayu, Jarayu and Shleshma are the three basic principles in the formation of Kala, these three structures can be compared with fiber, serous and mucous layers respectively [3].While describing \Kala, it is compared to be cores of a piece of wood or stem becomes exposed to view by cutting into it, so the Dhatu of the body can be seen by removing the successive layers. These Kala are extensively supplied with Snayu bathed in Jarayu and encased in Shleshma[4]. According to Acharaya Vagbhata internal part Ashaya containing Kleda undergoes Pakwa (differentiation) process and forms Kala[5]. It covers the internal and external layers of the organ, and it may separate the muscle. It helps for holding, movement; supporting, absorption and lubrication in the different parts of the body [6].There are seven Kala explained Ayurved Samhita.

Pittadhara Kala: Among all Kala Pittadhara Kala is sixth one located in between Amashaya and Pakwashaya which is also a location of Grahani, which is correlated as small intestine [7]. Function of Grahani is to store the Chaturviddha Ahara propelled from the Amashaya and on its way to the Pakvashaya[8] and also to process complete digestion, assimilation and absorption of food with the help of Pachaka Pitta which is secreted by Pittadhara Kala[9]. Location of Pachakagni is Grahani which helps in digestion of food [10] and converted it into Ahar Rasa which is absorbed by the Pittadhara Kala for the further nourishment of the seven Dhatu[11].

Majja Dhatu: According to Ayurveda Majja Dhatu is the sixth Dhatu which is located inside cavities of long bones which can be correlated as bone marrow [12]. The Vayu Mahabhut creates spaces in the bone and these spaces are filled up with the Snigdhaamsa of Meda as a Majja[13]. The function of Majja Dhatu is to provide unctuousness, strength and nourishment to Shukradhatu and fills Asthi Dhatu[14].

Pittadhara kala as majjadhara kala: Acharya Dalhan had stated that Pittadhara Kala as Majjadhara Kala [15], during description of Sarpa Vishvegawastha (Symptoms of Snake poisoning).When Sarpa Visha (Snake poison) enters into sixth Kala i.e. Majja Dhara Kala it vitiates Grahani and show the symptoms like heaviness in the body, dysentery, pain in heart and syncope [16].

Small Intestine: Small intestine is a part of intestine located between stomach and large intestine. It is divided into three parts i.e. duodenum, jejunum and ileum. The intestinal wall has serous, muscular, sub mucous and mucous layers. The sub mucous is a loose connective tissue carrying blood vessels, lymphocytes and nerves. The mucosa of the small intestine is lined by a simple columnar epithelium which consists primarily of absorptive cells i.e. enterocytes with scattered goblet cells and occasional enteroendocrine cells. The enterocytes secrets enzymes, goblet cells secrets mucus, enteroendocrine cells secretes intrinsic factor of castle, paneth cells secrete cytokines and Brunner glands secrets mucus and enzymes[17]. The columnar epithelial cells forms circular folds and the whole surface is covered by filiform or linguiform intestinal villi. The circular folds are large, crescentic folds of mucosa which project into the intestinal lumen. These folds slow down the passage of contents and increase the absorptive surface. Intestinal villi are highly vascular processes just visible by the naked eye and project from the entire intestinal mucosa. Small intestine is the major site of digestion and absorption from where all nutritive substances are absorbed like vitamin B12, folic acid, iron, cobalt, copper, manganese, calcium and proteins [18].

Absorption of vitamin B $_{12}$ [19]: Vitamin B_{12} is called extrinsic factor since it is obtained from dietary supplement. Its absorption from intestine requires the presence of intrinsic factor of castle which is secreted by parietal cells of gastric gland and makes it available for absorption by the small intestine. Vitamin B_{12} is important for the formation and maturation of red blood cells. Within the stomach, the Vitamin B_{12} is released from the food by photolytic enzymes (proteases). The free Vitamin B_{12} now combines with R binders obtained from saliva. In the small intestine, pancreatic enzymes remove 'R binders' and the free Vitamin B_{12} now combine with IF. IF is secreted by parietal cells of the stomach which secretes HCL. The Vitamin B_{12}-IF complex is resistant to digestion and travels down to reach lower part of ileum. In the membrane of the epithelial cells of the terminal part of ileum receptors for Vitamine B_{12}-IF complex exist the complex is taken up by cubilin part of these receptors, and the complex is absorbed by the enterocytes. After absorption from the intestine, Vitamin B_{12} being bound with transcobala- min II (β globulin) goes to the liver where it is stored. From the liver, the Vitamin B_{12} goes to red bone mar- row when the need of Vitamin B_{12} is very high.

Absorption of Iron [20]: Iron is important for the formation of hemoglobin. Dietary iron is available in two forms called heme and non heme. Iron is absorbed mainly from the duodenum of the small intestine through the intestinal cells called as enterocytes by pinocytosis and transported into the blood. Bile is essential for the absorption of the iron. Hydrochloric acid from gastric juice makes the ferrous iron soluble so that it could be converted into ferric iron by the enzyme ferric reductase from enterocytes. From enterocytes, ferric iron is trans- ported into the blood by a protein called ferroportin. In the blood ferric iron is converted into ferrous iron and transported into the blood.

Absorption of Folic Acid [21]: The form of folic acid occurring naturally in food is called folate. It is essential for the formation of DNA, RNA and metabolic amino acids. Folic acid is essential for final maturation of the red blood cells folate is mainly absorbed in the duodenum and jejunum.

Bone Marrow [22]: Bone marrow is a semisolid tissue which may be found within the spongy or cancellous portion of bones which is the site of new blood cell formation. Pluripotent

Hemopoietic Stem Cells, are the primitive cells in the bone marrow, which give rise to the blood cells. In early stages, the PHSC are not designed to form a particular type of blood cell hence the name uncommitted PHSC. When the cells are designed to form a particular type of blood cell, the uncommitted PHSCs are called committed PHSCs. The different committed stem cells, when grown in culture, will produce colonies of specific types of blood cells. Committed stem cell that produces erythrocytes is called a colony-forming unit-erythrocyte (CFU-E).

Erythropoiesis: Erythropoiesis is the process of the origin, development and maturation of erythrocytes. Site of erythropoiesis changes according to age. It takes place in red bone marrow from last three month of intrauterine life to long bones upto age 20 and in membranous bone after age 20[23]. Bone marrow contains Hemopoietic stem which are capable of self-renewal and differentiating into specialized cells i.e eryrthopcytes also known as uncommitted Pluripotent Hemopoietic Stem Cells (PHSC). When uncommited Pluripotent Hemopoietic Stem are able to differentiate into specific cells they are called as committed PHSCs. Committed PHSCs is of two types out of which Colony forming blastocytes give rise to myeloid cells. Myeloid cells are the blood cells which gives rise to Colony forming unit-erythrocytes (CFU-E) which develops into erythrocytes by erythropoiesis[24] .

Changes during Erythropoiesis [25]

Cells of CFU-E pass through different stages and finally become the matured RBCs. During these stages four important changes are noticed.

1. Reduction in size of the cell (from the diameter of 25 to 7.2 µ)
2. Disappearance of nucleoli and nucleus.
3. Appearance of hemoglobin.
4. Change in the staining properties of the cytoplasm.

Factors necessary for erythropoiesis [26]

1. General factors: Erythropoietin, Thyroxin, Hemo-poietic growth factors and Vitamins
2. Maturation factors: Vitamin B_{12}, intrinsic factor and folic acid are necessary for the maturation of RBCs.
3. Factors necessary for hemoglobin formation:

Stages of erythropoiesis[27]

Various stages between CFU-E cells and matured RBCs are –

1. Primary erythroblast
2. Early normoblast
3. Intermediate normoblast
4. Late normoblast
5. Reticulocyte
6. Matured erythrocyte

Primary erythroblast (Megaloblast)[28]: It is the first cell derived from CFU-E having large size with diameter of about 20µ, having large nucleus occupies the cell almost completely. Proerythroblast multiplies several times and finally forms the early normoblast. Synthesis of hemoglobin starts in this stage. Erythroblast requires folate and vitamin B_{12} for proliferation during their differentiation. Vitamin B_{12} and folate helps to make DNA, the genetic material in all cell. Deficiency of vitamin B_{12} and folate inhibits purine and thymidylate synthesis, impared DNA synthesis would be expected to result in chromosomal breakage and possibly nuclear damage causes erythroblast apoptosis resulting in anaemia from ineffective erythropoesis. Erythroblasts requires large amount of iron for hemoglobin synthesis which starts in this stage .

Early normoblast[29]: It is smaller than Proerythroblast with a diameter of about 15µ. In the nucleus, the nucleoli disappear, con- densation of chromatin network occurs which is essential for cell differentiation and liberate more spaces for hemoglobin enrichment.

Intermediate normoblast [30]: It is smaller than the early normoblast with a diameter of 10 to 12µ. The nucleus is still present; the chromatin network shows further condensation. Hemoglobin starts appearing.

Late normoblast[31]: It is smaller than intermediate normoblast with a diameter of about 8 to 10µ. Nucleus becomes very small with very much condensed, dark and clumped chromatin network, ready to be extruded. Once it is extruded, the cell is known as a reticulocyte. Quantity of hemoglobin increases. In the final stage of late normoblast just before it passes to next stage, the nucleus disintegrates and disappears.

Reticulocyte[32]: In this stage RBCs are immature and slightly larger than matured RBCs. The cytoplasm contains the reticular network which is formed by remnants of disintegrated organelles so the cell is called reticulocyte. During this stage the cell enter the blood capillaries through capillary membrane from the site of production.

Matured erythrocyte[33] : Reticular network disappears and the cell becomes the mature RBC and attains the biconcave shape with size 7.2µ diameter. The matured RBC is with hemoglobin but without nucleus. Folic acid works closely with vitamin B_{12} in making red blood cells by DNA formation and overall maturation process of RBC and helps iron function properly in the body. The normal proliferation of cells depends on adequate folate and vitamin B_{12}. Folate is necessary for efficient thymidylate synthesis and production of DNA. Vitamin B_{12} is needed to successfully incorporate circulating folic acid into developing RBCs, retaining the folate in the RBC.[34]

DISCUSION

'*Dhatwashayanter Maryada'* the one which separates *Dhatu* And *Ashaya* is defined as *Kala*. The *Ashaya* is cavity which gives *Ashraya* to the *Dosha*, *Dhatu* and *Mala*. *Snayu*, *Jarayu* and *Shleshma* are the three basic principles in the formation of *Kala*, these three structures can be compared with fiber, serous and mucous layers respectively which covers *Dhatu* and separates it from *Ashaya*. *Pittadhara Kala* is sixth *Kala* present between *Amashaya* and *Pakwashaya* i.e. *Grahani*. Process of digestion of food takes place in the *Grahani* with the help of *Pachaka* Pitta *and Ahar Rasa* get formed as terminal product of digestion of food. *Ahar Rasa* is absorbed by the *Pittdhara Kala* and transported to the different *Strotasa* for the formation of respective *Dhatu*. *Grahani* which is prime location of *Pittadhara Kala* and correlated as small intestine. Small intestine is the major site of digestion and absorption

from where all nutritive substances are absorbed like vitamin B_{12}, folic acid, iron, cobalt, copper, manganese, calcium and proteins. Intrinsic factor of castle is secreted by the parietal cells of the stomach and enteroendocrine cells of small intestine which helps in absorption of vita- min B_{12}. Structural abnormality in small intestine and gastric mucosa develops mal-absorption syndrome which includes crohn's disease, tropical sprue, due to all these conditions there is lack of absorp- tion of erythropoietic factors which are responsible for development and maturation of RBCs i. e erythropoiesis. *Pittadhara Kala* is considered as *Majjadhara Kala* so Functional status of *Pittadhara Kala* affect formation of *Majjadhatu* and overall function of *Majjadhara Kala*. *Majja Dhatu* is correlated with bone marrow which is present in cavity of long bones where erythropoiesis occurs. Any kind of disorder in bone marrow affects oveall process of erythropoiesis and resulting into various types of anemia. Protein digestion, formation and absorption of amino acid takes place in the small intestine which are necessary for the formation of hemoglobin during erythropoiesis. Also Vitamin B_{12} and folic acid are absorbed in small intestine which is utilized in the bone marrow during first stage of erythropoiesis i.e. megaloblast and these helps to make DNA a genetic material. Lack of these vitamins causes diminished DNA and consequently failure of nuclear maturation and division of RBC. Small intestine is the major site of absorption of all nutrients where as bone marrow is the site of production of blood cells. Efficient absorption of vitamin B_{12}, folic acid and iron, which are the influencing factors of blood formation results in healthy and matured RBCs in bone marrow by the process erythropoiesis.

Conclusion

Dhatwashayanter Maryada' the one which separates *Dhatu* And *Ashaya* is defined as *Kala*. *Snayu*, *Jarayu* and *Shleshma* are the three basic principles in the formation of *Kala*, these three structures can be compared with fiber, serous and mucous layers respectively which covers *Dhatu* and separates it from *Ashaya. Pittdhara Kala* is sixth *Kala* located between the *Amashaya* and *Pakvashaya* i.e *Grahani*. *Grahani* plays important role in the digestion, absorption of food and formation of *Ahar Rasa* with the help of *Pachak Pitta* which is transported to different *Strotasa* for *Dhatu* formation. *Grahani* is correlated with the small intestine which is a major site for digestion and absorption of proteins, Vit B12, Folate, Iron, Nickel,Cobalt which plays important role in the erythropoiesis. Erythropoiesis is the process of the origin, development and maturation of erythrocytes. It includes formation of erythrocytes from the PHSC by differentiation and maturation at the bone marrow. *Pittadhara Kala* is considered as *Majjadhara Kala* by *Acharya Dalhana*. *Majja Dhatu* is correlated as bone marrow. So from current study it can concluded that *Pittadhara Kala* plays important role in the erythropoiesis by absorption of essential factors like Proteins , Vit B12, Folate, Iron, Nickel, Cobalt which are necessary for DNA formation, maturation of RBC. and as a *Majjadhara Kala* it is involved in the formation of *Majja Dhatu* which is considered as bone marrow and it is site for erythropoiesis.

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