JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON ENDOTHELIAL DYSFUNCTION IN LIVER CIRRHOSIS W.R.T RAKTADHARA KALA.

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ABSTRACT

Background: The lives of the people suffering with Chronic liver cirrhosis has changed with the advent of Liver transplants. Liver transplants is on the rise in past few years due to increased incidence of NAFLD and Alcoholic liver disease, but Patients with long term coagulopathy or biliary sepsis (endotoxemia) do not warrant for transplant or fail post-transplant in most cases. Their line of treatment for cirrhosis does not reverse the organ damage but treat decompensation symptomatically. Here the Evolved Ancient wisdom of Ayurveda plays a major role that mentions *Raktadhatu chikitsa* in Liver cirrhosis. There is *Rakta dhatu dushti* in *Yakrut dushti*, as *Yakrut* is the moola sthana of *Raktavaha strotas* and *Raktadhara Kala*. We aimed to study the concept of *Raktadhara Kala* by comparing it with the endothelium. Method: The is a review on the various research articles on *Kala sharir* and coagulopathy in Liver cirrhosis. The concept of *Kala Sharir* was reviewed from Ancient texts. And an inference was drawn. Conclusion: We found that in Liver cirrhosis there is coagulopathy due to endothelial dysfunction and can be compared with *Raktadhara Kala*. Further research in this area could lead to new insights into the functioning of the human body and the development of new therapies

KEYWORD :

Liver cirrhosis, coagulopathy, kala, endothelial dysfunction, Rakta dhatu dushti

INTRODUCTION :

Liver cirrhosis is a major issue of public health, being responsible for approximately 1.2-1.3 million deaths per year worldwide, while it appears to be among the 10 most common causes of death in several countries [(i)]. The prevalence of cirrhosis is difficult to be evaluated because of the asymptomatic initial stages; thus, it was estimated at around 0.3% in surveys but at 4.5-9.5% in autopsy studies in the general adult population [(ii)]. The most common causes of cirrhosis are chronic hepatitis B, chronic hepatitis C, alcohol-associated liver disease and non-alcoholic fatty liver disease [(iii)]. The lives of the people living with disability adjusted years of life with liver cirrhosis changed with Liver transplant. Lately, there has been a rise in the transplants due to increased incidence of Alcoholic and NAFLD liver disease [iv]. But still,

transplant is not always a choice as it is expensive and donors are not easily available. It's been noted that transplants of patients of decompensation with long term coagulopathy or biliary sepsis (endotoxins) either do not make it till transplants or do not succeed post transplants in most cases. Coagulopathy is mostly seen in Alcoholic liver disease. Ayurvedic literature is a treasure of concepts. *Acharya Sushrut* in *Sharirsthan* has studied the human body precisely and mentioned concepts that are not known to modern science, like *strotas, kala, marma* etc, that may help treat rare diseases, like in case of liver disease allopathic medicine does not have a line of treatment that reverses cirrhosis or treats coagulopathy, here the concept of (*Avayav Utpatti*)Liver being produced by *Rakta dhatu*, *Yakrut* is the *moola sthana* of *Rakta dhara kala* and *Raktavaha strotas* plays a vital role.

The concept of *Kala Sharir* is unique. The word *Kala* is derived from a *Pali*-English dictionary means a small part of anything or portion of the whole. *Kala* is described as a limiting membrane or layer situated between Dhatu (vital elements) and Aashaya (cavities that hold the vital elements). There are seven *Kala* in the body, which are the substrata of the elements or vital elements of the human body.

Although many terminologies like *Kandara, Kurcha, Mansarajju, Sanghat, and Simanta* are described in *Ayurveda Sharir*, there is no established clinical significance of *Kala sharir* to date. However, understanding the concept of *Kala* can lead to a better understanding of the functioning of the human body and the development of new therapies. In this review, we aim to provide a comprehensive understanding of the concept of *Kala* in *Ayurveda*, its anatomical and physiological relevance, and its clinical implications.

MATERIAL AND METHODS:

The materials and methods for this study involved a review of various classical texts including *Charaka Samhita*, *Sushruta Samhita*, *Ashtanga Sangrah*, *Ashtanga Hridaya*, *Bhavprakasha*, and *Sharangdhar Samhita*. Additionally, evidence-based resources such as journals, books, and data-based information from modern texts were reviewed. The focus of the study was on *Kala Sharir*, and therefore contemporary anatomical literature, especially histology, journals, articles, internet material, and previous research papers related to this subject were also reviewed. The review of these materials and literature was used to provide a better understanding of *Kala Sharir* and its importance in the context of Ayurveda.

LITERATURE REVIEW

The literature review reveals that *Kala Sharir* is a concept described in various classical Ayurvedic texts, including *Susrutha Samhita, Ashtanga Sangraha, Ashtanga Hridaya, Bhavprakasha,* and *Sharangdhar Samhita.* The term *"Kala"* is used in different meanings in these texts, including indistinct, unit of time, minute, and membrane. In the context of *Sharir*, *Kala* refers to a thin membrane, which lines the internal cavity of the *Ashayas* (organs that hold the vital elements), organs, blood vessels and fibrous capsule of the joints and so on. *Kala* separates *Dhatu* and *Ashaya*. The *Ashaya* is the cavity that gives *Ashray* to *Dosha Dhatu* and *Mala*. The *Dhatu* lives in *Ashaya* and the inner lining of the *Ashaya* is called as *Kala*.[v]

Literature explains *Kalas* as when we cut a piece of wood, the cross section shows its internal structures with its different layers and parts. Similarly, on cutting Mansa we see the *(Rakta) Dhatu*. It means that *Dhatu* are principle factors of the body and they are deep seated. We incise the outer layer to reveal the *Dhat*u. These outer layer of covering are *Kala*.[vi]

Acharyas say that the process of *Dhatu* formation takes place in many stages. *Dhatu* begins as a liquid called *Dhaturasa*, transformed into the subsequent *Dhatu*. During this process, some *Kleda* remains between *Dhatu* and *Ashaya*, which is not converted into the previous or next *Dhatu* and remains in very less quantity, called *Kala*[vii].

The muscle layer that *Kala* is spread out like a membranous/fibrous structure (*Snayu-Pratichanna*) or resembles an amniotic membrane (*Jarayu-Santat*) or covered in mucus (*Shleshma- Veshtit*)[viii]. Membranous structure signifies structural support, amniotic membrane signifies barrier/selective permeability, and mucus signifies lubrication and nutrition.

In the description of how the *Visha* moves from one *Kala* to another, *Susrutha* has used the term *Asthidhara Kala* and *Majjadhara Kala* in place of *Purishadhara Kala* and *Pittadhara Kala*, respectively. The literature suggests that *Kala Sharir* has not been established with any clinical significance so far[ix].

There are seven *Kala* or limiting membranes that are the inner linings of various body cavities and tissues. *Sushrut*, has described *Kala* as sheath-like structures enveloped by *Shleshma* or mucoid material. In modern anatomical language, these structures are called mucous membranes. Epithelium is the layer of cells that covers tissue surfaces and body cavities opening to the outside. Embryological epithelium derives from all three germinal cells. Mesothelial cells line internal cavities and proximal parts of the urogenital tract lining, including the pericardial, pleural, and peritoneal cavities. Endothelium lines blood vessels and lymphatics.

The seven *Kala* described are[x]:

1. *Mamsadhara Kala*: This Kala is compared with the intramuscular septum that supports the muscles or inter muscular fascia as this *Kala* contains a network of veins, fibrous tissue, and arteries. Anatomically depicts the picture of a lotus stalk present in muddy water, whose roots spread at the base of the pond supporting the plant..

2. *Raktadhara Kala*: This *Kala* can be compared to the endothelial lining of arteries, veins, and lymphatics. The *Raktadhara Kala* lines the sinusoid in the liver, spleen and the blood vessels in the body[xi].

3. *Medodhara Kala*: This *Kala* supports the *Meda* or fat. Fat is found in the abdomen or peritoneal sac, and *Sushrut* has identified two types of *Meda*: *Sarakta Meda* (red bone marrow) found in short bones, and *Peeta Meda* (yellow marrow) found in long bones.

4. *Shleshmadhara Kala*: This *Kala* represents the synovial membrane in all the joints. It's compared to the lubricant in a wheel axis that permits the wheel to move freely. Similarly, *Shleshma* with the *Shleshmadhara Kala* allows all bony joints to move freely on their respective axes. This synovial membrane is lubricated with synovial fluid.

5. *Purishdhara Kala*: This *Kala* lines the *Pakwashay* mainly. It does *Sara Kitta Vibhajan*, extends from the *Unduk* (caecum) upto Rectum[xii]. *Pakwashay* is the *sthana of Vata dosha*, responsible for *Vata Dosha nirmiti* and maintenance of Asthidhatu *Purishadhara kala sa eva Asthidara kala.*[xiii] that is abnormality in this lining will cause bone density issues.

6. *Pittadhara Kala*: The *Pittadhara Kala* lines from *Amashaya to Pakwashay*, mainly located in the *Laghu Antra* (small intestine), which *Sushrut* has also described as "*Grahani.*" It acts on all types of food intake - *Asit, Khadit* (swallowed), *Peeta* (drunk-liquid), and *Leedh* (licked) - that enter the intestine. These are digested and absorbed in due course of time by the action of *pitta* or digestive enzymes. *Pittadhara kala sa eva Majjadhara Kala*[xiii], that is malfunctioning of this Kala causes Bone marrow related health issues.

7. *Shurkadhara Kala*: The last and seventh *Kala* identified by *Sushrut* is *Shurkadhara Kala*, which is functional all over the body in all living beings. *Shukra* is used for estrogenic and androgenic hormones that circulate in the entire body. They have been compared to sugarcane juice or Ghee present in milk. As these items cannot be independently identified in milk, similarly *Shukra* in the form of hormones cannot be isolated from the body, but its action can be observed

***Raktam Jeeva iti sthithi*.. hence, *Raktadhara Kala* is further studied as,**

Rakta dhara *Kala* is second *Kala*, which remains deep to *Mamsadhara Kala*. *Sira, Yakrut* and *Pleeha* are the locations of *Rakta* along with *Raktadhara Kala*. Gives an example, incision of a plant, which produces exudate white milky substance oozes out and when we incise skin, blood oozes out in the same way.[xiv]

Histological studies on Kala to correlate it with endothelium,

Sira,

There are 2 types of arteries,

-Elastic arteries (large or conducting vessels)

-Muscular arteries (medium arteries)

The muscular arteries can be taken as *Sira* and the elastic arteries as *Dhamanis*. Action of *Dhamanis* (pulsation) is seen in elastic arteries. *Viddha Lakshanas* of *Strotas* also support this inference. The *viddha lakshanas* of *Raktavaha strotas* are *Shyavangata, Panduta* and *Shonitagamanam* (bleeding). When *Raktadhara Kala* is cut, the blood oozes out, if the bleeding is not forceful it can be capillary bleed. Exchanges between blood and tissue take place through the walls of capillary plexus. The walls of capillary are formed essentially by endothelial cells that are lined on the outside by basal lamina.[xv]

Yakrut and Pleeha

In some tissues the work of exchange is in vessels that are somewhat different capillaries and are called sinusoids. Sinusoids are seen in organs made up of cords or plates of cells. The organs made of sinusoids are, liver, the cortex of adrenal gland, the pituitary gland, the parathyroid gland, spleen, the bone marrow and carotid body.. The walls of sinusoids are made up of endothelial cells supported by a layer of connective tissue. Their walls are perforated so that blood comes in contact with the walls of tissue. Sinusoids are broader than capillaries. The lumen is irregular. Because of these features blood flow through them is slightly sluggish. Thus when ruptured bleed profusely.[xvi]

Thus, Rakta dhara Kala can be correlated with Endothelium that lines the Liver, Spleen, Blood vessels and lymphatic.

Endothelial Cells in Liver

The liver is the central metabolic hub for carbohydrate, lipid, and protein metabolism. It is composed of four major types of cells, including hepatocytes, endothelial cells (ECs), Kupffer cells, and stellate cells. Hepatic ECs are highly heterogeneous, representing the second largest population of cells in liver. The majority of them line hepatic sinusoids known as liver sinusoidal ECs (LSECs). Immuno-cytochemical staining and quantification revealed that hepatocytes and ECs constitute ~52% and 22% of all labelled cells, respectively.

Endothelial cells in the liver, called liver sinusoidal endothelial cells (LSECs), have many functions, including:

- **Maintaining homeostasis**

LSECs help maintain hepatic homeostasis by regulating vascular tone, controlling inflammation, and regulating the coagulation cascade.

- **Paracrine effects of LSEC**

Perturbed EC communication with other cell types plays a key role in the development of diseases such as obesity. In liver, ECs can impair insulin action in hepatocytes via tyrosine nitration of insulin receptors, leading to impaired ability of insulin to suppress glucose production[xvii].

- **Immune regulation**

LSECs play a key role in maintaining immune homeostasis in the liver. They also mediate the immune response during liver injury.

- **Regulating the exchange of substances**

LSECs form a permeable barrier between blood cells and hepatocytes. They also contain many fenestrae, which are open channels that allow substances to be exchanged between the blood and liver.

- **Regeneration**

LSECs are involved in liver regeneration after acute liver injury or partial hepatectomy.

- **Pathology**

LSECs can play a role in the initiation and progression of chronic liver diseases, including hepatocellular carcinoma. During liver injury, LSECs can become dedifferentiated and acquire pro-inflammatory, prothrombotic, and vasoconstrictor properties.

Morphology of LSEC –

LSECs are the most abundant non-parenchymal hepatic cell population. They have unique structural and phenotypic features, including open fenestrae and a lack of a basement membrane.

DISCUSSION

Endothelial dysfunction -.

Yakrut Pleeha and *Sira* are the *Moolasthana* of *Raktadhara Kala*, that is the endothelium lines their sinusoids and the blood vessels. The endothelium is the largest organ and encompasses > 10^{13} endothelial cells in the body, its able to generate both vasodilator [nitric oxide (NO), endothelium derived hyperpolarising factor (EDHF) and prostacyclin] and vasoconstrictor (endothelin-1, norepinephrine, leukotriene, thromboxane A_2 and angiotensin II) substances and is essential for hepatic vascular homeostasis. Endothelium serves as a barrier to separate blood from the underlined tissue and thus maintains homeostasis at the vascular wall during physiological condition [xviii]. The salient features of normal healthy endothelium which including, regulation of vascular permeability, decrease in vascular tone, reduce in platelets adhesion and aggregation, prevention of thrombosis, inhibition of smooth muscle cell proliferation, inflammation and restricting leukocyte adhesion inflammatory processes, and innate and acquired immunity [xix]. Any impairment of endothelium, caused by physical or chemical stimuli, can lead to endothelial dysfunction, which typically includes an imbalance between vasoconstricting and vasodilating agents, procoagulant and anticoagulant factors, or growth promoting and inhibiting substances [xx] Indeed, many of these functions are mediated by endothelium driven Nitric Oxide [xxi]. The term **endothelial dysfunction (ED)** implicate a loss of function of numerous activities of the endothelium [xxii], mainly characterised by impairment of the production and release of endothelium driven vasodilatory factors including NO [xxiii]. The hepatic vascular bed of cirrhotic liver exhibits ED and is now considered to play a key role in the initiation and advancement of liver cirrhosis [xxiv]. The intrahepatic vasculature also displays increased sensitivity to vasoconstrictors in cirrhosis [xxv]. Furthermore, ED is also a common index for a wide variety of pathological conditions such as chronic renal failure, atherosclerosis, hypercholesterolemia, hypertension, diabetes and coronary artery disease [xxvi].

Nitric oxide (NO) is the vasoactive agent most commonly linked to endothelial function, since impaired NO bioavailability is the hallmark of endothelial dysfunction [xxvii].

From a circulatory standpoint, liver cirrhosis is characterized by significant dysregulation, related to imbalance of several vasodilating agents, including NO [xxviii]. According to current knowledge, reduced NO bioavailability and oxidative stress in the intrahepatic vascular system results in increased intrahepatic resistance and portal hypertension. On the other hand, several systemic vascular beds were shown to overproduce NO, a fact linked to arterial vasodilation and a hyper dynamic state[xxix]. In contrast to portal vein and macro vascular hemodynamic alterations, which have been rather well described, the peripheral microcirculatory structure and function in cirrhosis are less well studied [xxx]. As microcirculatory endothelial dysfunction is associated with increased target organ damage, cardiovascular events and mortality in the general and other populations, there is a need for a better description of the status and the impact of peripheral endothelial dysfunction in cirrhosis [xxxi].

CONCLUSION

Thus, *Raktadhara Kala* can be correlated with Endothelium that lines the sinusoids and blood vessels in the body. Deeper understandings of *Yakrut Sharir*, *Rakta dhatu*, *Raktavaha strotas* and *Raktadhara Kala* will lead to better out comes in Liver cirrhosis and reduce the mortality related to it.

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