



Review Article

ENDOTHELIAL DYSFUNCTION AND DIABETES; AN AYURVEDIC CONCEPT

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ABSTRACT

Diabetes mellitus is associated with an increased risk of cardiovascular disease, even in the presence of intensive glycaemic control. Both diabetes and insulin resistance bring about an amalgam of endothelial dysfunction and it will abate the anti-atherogenic role of the vascular endothelium. In patients with type 2 diabetes both insulin resistance and endothelial dysfunction appear to lead up to the development of undisguised hyperglycaemia. Hence, in patients with diabetes, endothelial dysfunction may be a censorious early intention for preventing atherosclerosis and cardiovascular disease. For the assessment endothelium-dependent vasodilatation Coronary and peripheral circulations are used. In Ayurveda, endothelial dysfunction can be correlated to *Rakthavaha srotho dushti*. There are several aetiological factors similar in both *Prameha* and *Rakta dushti*. The factors which got vitiated (*Dooshya*) in *Prameha* are *Mamsa*, *Meda*, *Rasa*, *Rakta*, *Shukra*, *Lasika*, *Vasa*, *Majja* & *Oja*. Amongst all *Meda* & *Mamsa* are main vitiated factors (*Dooshya*) while *Rakta* is one of the *Dooshya* initially. During nourishment, *Rakta* is nourished prior to *Meda* & *Mamsa*. Further it nourishes *Meda dhatu* too. Endothelial dysfunction is reversible in early stages so that many *Rasayana* drugs mentioned in the Ayurveda can be used here. In the present review briefly outlines some basic concepts of endothelial structure and function, and its dysfunction, relation with diabetes and its Ayurvedic concepts and management.

INTRODUCTION

The endothelium, a monolayer of endothelial cells, constitutes the inner cellular lining of the blood vessels (arteries, veins, capillaries) and the lymphatic system, and therefore is in direct contact with the blood/lymph and the circulating cells.^[1] The apical surface of the endothelium is covered by a layer called the endothelial glycocalyx, which consists of a mosaic of glycoprotein and proteoglycans and glycosaminoglycan chains. The endothelial glycocalyx, together with secreted proteoglycans and other absorbed plasma proteins including albumin, forms the endothelial surface layer^[2].

Normal Endothelial Functions

The major functions of endothelial cells including maintenance of vascular tone, cell adhesiveness, platelet aggregation, leucocyte trafficking, coagulation cascade, inflammation, permeability, regulation of thrombosis and fibrinolysis.^[3]

a) Regulation of Vascular Tone: The endothelium releases various vasoactive factors. Vaso active factors either be vasodilatory factors like prostacyclin (PGI₂), nitric oxide (NO), endothelium derived hyperpolarizing factor (EDHF) or vasoconstrictive factors like thromboxane (TXA₂) and endothelin 1 (ET-1). Nitric oxide is an endothelium dependent vasodilator of the underlying smooth muscle. NO has been shown to play an important role in the maintenance of basal vasodilator tone of the blood vessels.^[4] Imbalance between vasodilation and vasoconstriction is caused by the damage of the endothelium which results in the initiation of a stream of events like platelet aggregation, increased endothelial

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permeability, leucocyte adhesion and generation of cytokines^[5].

b) Coagulation and Fibrinolysis: Endothelial cells have major roles in regulating haemostatic balance, preventing the activation of thrombin and inhibiting platelet adhesion, thereby mediating anticoagulant activity.^[6]

c) Cell Growth and Differentiation: The synchronised regulation of vasculogenic or de novo differentiation of bone marrow-derived endothelial progenitor cells (EPC), that is, angioblasts into endothelial cells followed by angiogenesis, is required for the vascular system development.^[7]

d) Adhesion and Permeability: Endothelial cells produce specific adhesion molecules, namely E-selectin, intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM), for the regulation of cell adhesion and permeability.^[8]

Endothelial Dysfunction

Endothelial dysfunction is a condition in which the endothelial layer of the arteries fails to perform all of its important functions normally. And is characterized by reduction of the bioavailability of vasodilators, particularly nitric oxide (NO), and/or an increase in endothelium derived contracting factors. The resulting imbalance leads to an impairment of endothelium- dependent vasodilation, which is the functional characteristic of endothelial dysfunction.^[9] Endothelial dysfunction is triggered by a number of factors including turbulent blood flow, shear stress, hypoxia, ageing, hyperglycaemia, dyslipidaemia and hypertension^[10]. In diabetes, the pathophysiology of endothelial dysfunction is the primary event in the development of microvascular and macrovascular complications. The microvascular complications in diabetes comprises long term complications like diabetic retinopathy, Nephropathy and Neuropathy. The macrovascular complications includes cardiovascular, cerebrovascular disease and stroke.^[11]

Endothelial Dysfunction and Diabetes

Regulation of the glucose metabolism in the endothelial cells is carried out by vascular homeostasis by balancing insulin levels and stimulating glucose transport^[12]. Elevated glucose interrupts the vascular homeostasis and leads to both microvasculature and macrovasculature modifications by inducing the phenotypic switch and altering intracellular signalling pathways^[13]. The mechanisms such as oxidative stress, inflammation, and chronic alterations in the hemodynamic balance are accountable for the development of endothelial dysfunction in type 2 diabetes. Endothelial activation and dysregulation determining factors includes: increased arginase, decreased tetrahydrobiopterin (BH4) bioavailability and eNOS uncoupling, increased ROS production, increased asymmetric dimethyl arginine, decreased NO

bioavailability, increased glycation and expression of receptor for advanced glycation end products (RAGE), nuclear factor κ B (NF κ B) activation, suppression of Kruppel-like Factor 2^[14] and phenotypic changes in perivascular adipose tissue which leads to low grade inflammation and reduced adiponectin secretion^[15].

In diabetes, there will be an interaction between metabolic abnormalities and vascular dysfunction. Inflammation plays significant role in it. In patients with diabetes and obesity, the levels of circulating inflammatory markers are elevated which promotes endothelial dysfunction. In the diabetic terrain, dyslipidaemia and hyperglycaemia foster several intracellular and extracellular events and affect different cells in the vascular wall, give rise to endothelial dysfunction^[16].

The metabolic contexture in diabetes, i.e., insulin resistance, hyperglycaemia, hyperinsulinemia and obesity persuade a broad spectrum of events.

a) Hyperglycemia and endothelial dysfunction: Hyperglycemia is creating imbalance between accumulation of ROS as well as RNS (reactive nitrogen species, resulting in endothelial dysfunction) and NO bioavailability which triggers the vascular damage thought to trigger vascular damage.

b) Insulin resistance and endothelial dysfunction: One of the main features of T2DM is Insulin resistance, that means reduced ability of insulin to promote glucose uptake in multiple organs like adipose tissue, heart and skeletal muscles to restrain the hepatic glucose output. Excessive release of free fatty acids in adipose tissue and proliferation of vascular smooth muscle cells are stimulated by insulin resistance which eventually increases the oxidative stress.

c) Excessive free fatty acids and endothelial dysfunction: The reduced uptake by skeletal muscles and the excessive release from adipose tissue are caused by the increased circulating levels of FFAs. Excessive FFAs are the main reasons for impair normal endothelial function and lipotoxicity by same mechanisms and to the same extent as by glucotoxicity.

Assessment and Biomarkers of Endothelial Dysfunction in Diabetes Mellitus

Coronary and peripheral circulations are used for the assessment of Endothelium-dependent vasodilatation. Positron emission tomography, Doppler echocardiography and phase-contrast magnetic resonance imaging are the non-invasive tests for the evaluation of endothelial function. Invasive coronary angiography is the essential part for the evaluation of coronary endothelial function. Examination of the changes in diameter in response to intracoronary infusions of endothelium-dependent vasodilators is

done by using quantitative coronary angiography. Brachial artery ultrasound is the most commonly used measure in peripheral Circulation. Strain gauge venous impedance plethysmography is used for the assessment of the Peripheral vascular endothelial function [17].

Ayurvedic Aspect

By analysing above mentioned factors endothelial dysfunction can be correlated as *Rakthavaha srothodushti*. The *Raktha dhathu* which is also referred as 4th *Dosha* by basic principles of Ayurveda, is one of the functional element of body, of which formation, transformation and conduction is carried out by *Rakthavaha srothas*. According to *Susrutha*, *Rakthavaha srothas* or channels carrying blood are two in number and are rooted in *Yakrit* and *Pleeha* and *Rakthavahini dhamanis*[18] (The arteries transporting the blood). *Charaka* too has mentioned *Yakrit* and *Pleeha* as the root of *Rakthavaha srothas*[19]. Circulation of blood depends on the proper functioning of heart. For these various types of *Doshas* plays an important role. Function of pushing and pumping in appropriate manner is known as *Vikshepochita karma*.

The function of *Asrik sravana* is possible by the stimulation of the sympathetic supply to heart but also on the calibre of blood vessels. *Vyana* makes *rasa* to get forcefully ejected out of the heart and makes it circulate throughout the body. So sympathetic and para sympathetic control of heart can be included under functions of *Vyana vata*[20]. *Prana vayu* has the function of *Hridaya dharana* (it holds the function of heart)[21] and *Avalambaka kapha* has *Hridaya sandharana* function ie *Avalambaka kapha* with the help of *Annarasa* would protect and support the heart[22]. Heart supplies nutrition to all parts of body through circulation of blood.

Prameha and Raktha dushti

From the table-1 we can see that some of the etiological factors are common in both *Prameha* and *Rakthadushti*. In *Prameha* most of the etiological factors will cause *Kapha Medo dushti*. In *Ashtanga Hridaya sootrasthana*- chapter on *Siravyadha vidhi*, it is mentioned as “*Tat Pittashleshmalai Prayo dooshyathe, Kuruthe Tata*” that means *Raktha* usually gets vitiated by those that vitiate *Pitta* and *Kapha*[23].

Etiological Factors of <i>Raktha prakopa</i> [24]	Etiological Factors of <i>Prameha</i> [25]
<i>Theekshna, Ushna, Atilavana</i> <i>Amla, Katu, Kshara</i> <i>Dadhi</i> <i>Drava, Snigdha, Guru</i> <i>Bajatha cha atapa anala</i> <i>Chardhi vega pratighata</i>	In <i>Kaphaja prameha</i> <i>Dadhi, Drava ahara</i> In <i>Pittaja prameha</i> <i>Ushna, Amla, Lavana,</i> <i>Kshara, Katu</i> <i>Atitheekshna, Atapa</i> <i>Agni santhapa</i> In <i>Vataja prameha</i> <i>Vamana atiyoga</i>

Table -1

<i>Raktha pradoshaja vikaras</i> [26]	<i>Prameha</i>
<i>Kushta</i> <i>Visarpa</i> <i>Vidradhi</i> <i>Pidaka</i>	Skin manifestation of diabetes Like acanthosis nigricans, acrochordrons, Diabetic dermopathy etc <i>Prameha pidakas (Saravika, Kachapika etc)</i> Eruptive xanthoma

Chakrapani clearly explained about *Raktha dushti* in *Prameha* in the context of *Madhumeha*. Pathogenesis of *Madhumeha* mainly related with vitiation of *Raktha* and *Oja*. Consumption of dietetic regime and behavior factors that provoke *Vata* by properties like *Rooksha, Laghu, Kashaya, Tiktha* tastes causes provocation of *Vata*. This *Vata* spreads through the body and turns *Madhura* of *Oja* in to *Kashaya rasa*[27]. *Snigha* and *Soumyata* properties of *Oja* get transformed into *Rookshata*. This accumulated *Madhura* of *Oja* in circulation causes deterioration of *Raktha* because of *Abhishyandi* nature. This further amplifies liquidity in the channels compelling more

Drava dhathu to ooze in. When *Kapha Pittaja Prameha* in initial stages get ignored or not treated properly, there occurs further vitiation of *Mamsa* and *Sonitha*[28]. So, as *Madhumeha* getting more chronic and ignored, chances of *Raktha dushti* get prominent in that condition.

Rakthadushti will turn to the *Dushti* of *Rakthavaha srothas* also. (Can be considered as microvascular complication, endothelial dysfunction).

Management

Endothelial dysfunction is reversible in early stages, and strategies targeted at reducing cardiovascular risk factors such as controlling hyperglycaemia, cholesterol lowering, anti-hypertensive therapy, smoking cessation, ACE inhibitor therapy and physical exercise, also convert into an improvement in endothelial health.

The *Rasayana* drugs useful in complications of *Prameha* like microangiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, macroangiopathy are as follows:

Pippali- Due to *Katurasa* it does *Rasadhatwagnidipana*, it alleviates atherosclerosis

Guloochi- Reduces *Kledaka dushti* and is *Rasaraktha sudhikara*

Manjishta- *Raktaprasadaka* and *Raktaposhakam*. It does *Raktaprasadana* through its *Vranasodhana* and *Vrana ropana karma*. *Ushna guna* of *Manjishta* destroys the *Styanata* of *Rakta dhatu* and improves *Rakthasamvahana kriya* thus preventing *Srothorodha*.

Lasuana- helps to reduce atherosclerotic build up (plaque) within the arterial system and lowers or helps to get regulate blood sugar.

Haritaki- in *Charaka chikitsa* first chapter, it has mentioned that along with *Prameha*, *Haritaki* prevents obstruction of the channels and feeling of coating in the heart and chest^[29].

CONCLUSION

Main functions of the endothelium include maintaining vascular homeostasis and preventing the development of atherosclerosis. Hyperglycaemia results activation of endothelial cells by various pathways resulting in endothelial dysfunction and vascular disease in particular microangiopathy and arterial stiffness. These concepts are already mentioned in Ayurveda also. In ayurveda there are various medicines described for the management of *Prameha*. By managing *Prameha* we can prevent further *Rakthadushti* and *Rakthavaha srothodusthi* also.

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