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Review Article

Conceptual analysis of diabetic retinopathy in Ayurveda

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ABSTRACT

Inclusion of *Prameha* among the eight major disorders in *Charaka Samhita* shows the importance of the disease given by ancient seers. The risk of development of blindness in diabetics increases by 20–25 times as compared to the normal population. High prevalence rate of Diabetic Retinopathy (34.6%), proliferative diabetic retinopathy (7%), diabetic macular edema (6.8%), and Vision threatening Diabetic retinopathy (10.2%) in diabetics was great concerns which led to search and analyze the disease process on the basis of modern pathogenesis and different *Timirvyadhi* mentioned in Ayurvedic authoritative texts. Thus the present study endeavors to discuss the similarities and differences among the various components of *Prameha*/*Madhumehajanya Timir* with Diabetic retinopathy and its stages. To establish a probable etiopathogenesis of the disease from Ayurveda prospective, all the important literature of both modern medicine and Ayurveda along with online sources were searched and analyzed. All the three *dosha* along with *Raktadosha* and *Saptadhatu* with four internal *Dristipatals* of eye are affected in *Madhumehajanya timir* in different stages of the disease. *Avarana* and *Dhatu kshaya* too have important role in development of diabetic retinopathy due to prolonged and uncontrolled hyperglycemia. *Agnimandya* related *Ama* formation has a role in pathology of diabetic retinopathy which is quite similar to oxidative theory of diabetic retinopathy explained in modern pathology. *Urdhwaga raktapitta*, *Ojas kshaya*, *Raktavritta vata*, and *Pranavritta vyana* are other causes in development of diabetic retinopathy.

1. Introduction

Diabetes mellitus has in recent times, gained importance as one of the most common, non communicable disease, which contributes to death and disability worldwide. Diabetes affects almost all aspects of intermediary metabolism and is also associated with accelerated aging of the cardiovascular system. Hence diabetes is best defined as a metabolic cum vascular syndrome of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both, leading to changes in both small blood vessels (microangiopathy) and large blood vessels (macroangiopathy) and which is often associated with long term damage, leading to malfunction and failure of various organs like eyes, kidneys, heart, nerves and blood vessels [1].

Diabetic retinopathy is a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with prolonged hyperglycemia and other conditions linked to diabetes mellitus such as hypertension, hyperlipidemia and proteinuria etc. [2]Almost all the patients with Type I diabetes develop retinopathy in about 15 years. In those with Type II diabetes, the risk of DR increases with the duration of diabetes, accompanying hypertension and smoking. Diabetics have a 20–25 times greater risk of blindness as compared to the normal population [3]. As far as the working class or industrial areas are concerned Diabetic Retinopathy is 2nd leading cause of blindness in working age group (<55 years old) in industrialized countries [4].

Diabetic Retinopathy (DR) is one of the major complications of diabetes mellitus. It is a leading cause of blindness in developed as well as developing countries. According to VISION 2020 (Working together to eliminate avoidable blindness) up to 80% of the world's blindness is avoidable. Avoidable blindness is defined as blindness which can be either treated or prevented by known, cost-effective

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means. Although there are many other causes of vision impairment, VISION 2020 seeks to address the main causes of avoidable blindness, in order to have the greatest possible impact on vision loss worldwide. Diabetic retinopathy is one among the target diseases for VISION 2020 [5].

The prevalence of DR, proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), and VTDR (Vision threatening Diabetic retinopathy) among individuals with diabetes is 34.6%, 7.0%, 6.8%, and 10.2%, respectively. Estimate shows that the number of people with DR will grow from 126.6 million in 2011 to 191.0 million by 2030, and the number of people with VTDR will increase from 37.3 million to 56.3 million, if no urgent action is taken [6]. Innovative alternative therapies and comprehensive approaches are needed to reduce the risk of vision loss by prompt diagnosis and early treatment of Vision Threatening DR (VTDR).

After viewing the magnitude of the problem of the disease, a comprehensive and thorough analysis of all the important literature of both modern and Ayurveda was done and online sources are searched to establish a probable etiopathogenesis of the disease on Ayurvedic prospective. Though there are no direct references are available regarding *Madhumeha/Prameha janya Timir*, enough evidences are available in all leading treaties of Ayurveda, which substantiate that *Timir* can be a complication of *Madhumeha*. In this review study many aspects of basic concepts of Ayurveda were analyzed to find out the probable etiology and pathogenesis of Diabetic retinopathy with probable correlation of different stages of the disease with different types of *Timir* described in Ayurvedic literature.

2. *Samprapti* (pathogenesis) of diabetic retinopathy

2.1. Role of Raktapitta in manifestation of diabetic retinopathy

Diabetic retinopathy basically a *Dristipatalagata roga* is mainly attributed to *Sira srotasabhisyandam* and *raktavaha sroto dusti* due to a variety of *Achakshyushya ahara* and *vihara karanas* especially in *Prameha* patients. In order to understand the *samprapti* of diabetic retinopathy in Ayurveda, general *samprapti* of eye disease must be considered. *Nidana* of endogenic eye diseases are mainly *Achakshyushya* factors which vitiates *Pitta*. The vitiated *Pitta* in turn vitiates the *Pitta vaha srothas*. Due to interconnection of *Pitta* and *Rakta*, which shares *Ashrya Ashrayee bhava*, the *raktavaha srotas* is also gets vitiated due to *Pitta* vitiation. As the *nidana* factors are *Achakshyushya*, the vitiated *pitta* and *rakta* have an affinity towards penetrating the eyes. Hence the vitiated *dosha* move towards the eyes through *Jatroordhwa srotas* and finally gets confined to the eyes, there is a stage when the *Sirasrothas* are deeply involved which is known as *Sira abhisyanda* [7]. The whole pathology of diabetic retinopathy which starts with *sroto dusti of Raktavaha srotas* manifested as microangiopathy in the form of *Attipravriti, Sanga* and *Granthi* as haemorrhages, exudates and venous beading in diabetic retinopathy respectively.

In this context of *Siroabhisyandam* in eye diseases the *Ashraya sthana* is *Srotas*, affected *dhatu* is *Rakta* and vitiated *dosha* is *Pitta*. *Prameha* brings out changes in the *dristipatalam* which greatly affects vision. In the initial stage, the etiological factors promote *utklesa* in the vessels which causes changes in the permeability of the vessels especially of head region which is the basic pathologic change for the development of eye diseases. If the stage of *Sira abhisyanda* continues it spreads to *netrasrotas* and the same vascular changes takes place in the vessels of eye, because *Achaksyushya* factors always have affinity towards the ophthalmic tissues. In the stage of *netraabhisyandam*, if there is further vitiation of *Pitta dosha*, the condition further aggravates and will be confined to *Dristipatalam*.

Few predisposing factors also influence the development of eye disease associated with prameha. These include- 1. *Pittaprakritti* of the patient. 2. Hereditary factors 3. Pitta Kapha predominant season, foods and psychological stress factors like *krodha, soka* etc., which contribute towards vitiation of *Pitta*. Vitiated *Pitta* reaches and amalgamated with *Rakta dhatu* due to similar properties. All these factors altogether promote prominent changes in the vessels of *Dristipatalm*. The texture of the vessels is damaged and hence the permeability increases. This results in leakage and hemorrhages from the blood vessels. The blood oozes out like sweat. This again correlates with pathogenesis of *Raktpitta*, specially quoted by *Charaka*. Due to lack of circulation there is localized hypoxia which results in development of new vessels. As these vessels are fragile they bleed easily. Exudates formation, neovascularization and proliferation of the tissues which leads to degenerative changes in the retina. In this context *Urdhwaga Raktapitta* can be correlated with Diabetic Retinopathy, as the seat of *Urdhwag Raktapitta* are all the seven natural openings of the head. And in eye, as the vessels are minute and due to *achakshyushya* factors the vessels of *dristipatala* or retina are affected mostly [Fig. A.1].

2.2. Avaranajanya, Dhatukshyajanya Timir and diabetic retinopahy

According to *Vagbhata*, *Madhumeha* is chronic progressive stage of *Prameha* and of two types: *Avaranajanya* and *Dhatukshyajanya* [8]. *Madhumeha* is *Vataja* type of *prameha* and *Vata* can be aggravated by two ways i.e. *Avarana* and *Kshaya* [9]. *Avritta vatajanya madhumeha* is *krichhrasadhya* and *dhatukshyajanya madhumeha* is *asadhya* (incurable). As per charak "*prameha anusanginam*" means diabetes is concomitant in nature. Thus diabetes remains always present with its complications. Due to both *avarana* and *dhatukshya* all the ten *dushyas* goes into state of depletion and produce symptoms according to the seat of that particular *dhatu*. In the case of Diabetic retinopathy main affected *dhatu* is *Rakta dhatu*, though all the *dhatus* gets affected and *srotas* affected are *Raktvaha*, *mamsavaha* and *medovahasrotas* mostly. List of *doshas*, important *dushya*, *dhatu kshaya* symptoms, *srotas* affected and their modern interpretation for pathogenesis of Diabetic retinopathy are mentioned in Table A.1.

2.2.1. Avarana

A. ***Pranavritta vyana***: *Pranavayu* acts like a controller. It is responsible for *Adana karma*. Sense organs perceive their objects with the help of *Pranavayu*. *Vyanavayu* is responsible for gati or conduction. Hence *vyanavayu* plays a significance role in *Rasavikshepana*. Conduction is not only related to cardiac cycle but all types of neural conduction should be considered. Whenever the controller *Pranavayu* will restrict the gati of conducting *vyanavayu*, the *Indriya* will not be able to perceive its *visaya*. It may happen in one *Indriya* (homonymous) or in all *indriyas* (heteronymous) together. If it happens in all indriyas it can be compared with the vegetative stage or deep coma. *Rasa-Rakta vikshepana* (blood circulation) is function of *vyanavayu*. In case of diabetic retinopathy vascular disorder may arise due to *Pranavritta vyana*. This initially causes retinal ischemia and followed with successive cascade of retinopathic changes like neovascularisation, cotton wool spots and intra retinal microvascular abnormalities (IRMA). Early break down of blood retinal barrier (BRB), hard exudates formation and macular edema are other symptoms to follow. Symptoms of *Pranavritta vyana* are *Sarva indriya sunyata*, *smriti kshaya* and *bala kshaya* and the treatment is *Urdwa Jatrugata cikitsa* (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 28:202; P 974). In

this stage *Nasya* (Trans nasal medication) can be employed to relieve the signs and symptoms of Diabetic Retinopathy.

B. ***Raktavritta vata***: Etiologies explained in *vidhisonitiya adhyaya* of *Charak Sutrasthan* are responsible for quantitative increase of *Rakta dhatu*, which impedes the movement of *Vata dosha* hence normal circulation is hampered and stagnation takes place leading to *Sanga* of *Raktavaha srotas*. Symptoms of *Rakatvrita-vata* are: *Twakmamsa antarajadaha* and *Raktayukta sotha mandala* (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 28:63; P 949). This type of symptoms can be correlated with general neuropathy; *Raktayukta sotha mandala* can be correlated with splinter haemorrhages and IRMA as well retinal edema. Most of the etiological factors responsible for *Raktaja vyadhi* have similarity with *madhumeha* and *prameha* etiological factors. *Akshiragam*, *Tamasyatidarshanam* and *Raktapitta* are described as *Raktaja vyadhi* in *Charak samhita*. These can be correlated with vision defects in diabetics due to microvascular complications. In diabetic retinopathy though initially *Raktakshya* and ischemia occur but later on blood circulation increases, which lead to haemorrhages and exudative features. Treatment of *Raktavritta vata* should be done as per *Vataraktachikitsa* (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 28:194; P 972) to normalize the movement of obstructed Vata dosha. And *Charak* has mentioned *Basti* as the best treatment for *Vatarakta* (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 29:88; P 998). Thus *Basti* (therapeutic enema) treatment can be administered in this type of pathological symptoms of Diabetic Retinopathy. *Avaranajanyasamprapti* and pathogenesis of Diabetic Retinopathy depicted in Fig. A.2.

2.2.2. Dhatukshaya

A. ***Sirasaithilya*** [10] is one of the major signs of *raktakshaya*as per Sushruta. Loss of pericytes and formation of microaneurysms are earliest signs of Diabetic Retinopathy. These can be correlated with *Sirasaithilya* due to *Raktakshaya*. First *Patala* consists of *rasa* and *rakta dhatu*, so manifestation of the disease is in the form of microaneurysms and less severe in nature, which are very similar to background Diabetic retinopathy or mild NPDR and symptoms of 1st *Patalagata Timir* appears in this stage. If *Raktakshaya* persists for long time, it may leads to hypoxia related neovascularization in Diabetic retina.

B. ***Dhamanisaithilya*** [10] is one of the features of *mamsakshaya*. This can be correlated with endothelial cell loss due to improper apoptosis and loss of capillaries, leads to early break down of blood retinal barriers and signs like dot/blot or flame shape hemorrhages appear in this stage. As 2nd *patala* consists of *sookshma rupi mamsa dhatu*, symptoms of 2nd *patalagata timir* seen in this stage. This stage may be correlated with mild NPDR or moderate NPDR depending upon the extent and severity of affected *dhatu*.

C. ***Sandhishunyata*** [10] is another feature of *medakshaya*, which may be correlated with junctional cell protein loss or cell adhesion defects and break down of BRB. Appearances of macular edema and exudates formation are prominent signs in this stage. 3rd *patala* consists of *Meda dhatu* and when *dhatu kshaya* reaches the 3rd patala symptoms of 3rd *patalagata timir* appears. On severity point of view this stage may be correlated with Moderate NPDR based on the extent of dhatu affected. 4th *patala* of *dristipatal* is *asthyasrita* in nature and loss of *asthi* and *majja dhatu* leads to symptoms of 4th *patalagata timir*.

D. ***Timiradarshana*** is one of the symptoms of *majjakshaya* (Gupta Atridev, 2008, Ashtanga Hridaya, Sootrasthan, 11:19; P 116) and thus leads to Vata kshaya. Depletion of marrow tissue leads to decrease in blood cells formation and results in hypoxic condition of retinal neurons. Axonal degeneration of retinal nerve fibers occur due to *Vata kshaya*, which may be correlated with hypoxia and this hypoxic axonal degeneration leads to formation of cotton wool spots or soft exudates in severe NPDR stages of Diabetic retina. In latent stages when *Sukradhatu* gets affected signs of paleness of retina and optic atrophy appears as *Panduta* is one of the features of *sukrakshaya* (Tripathy Brahmananda, 1999, Caraka Samhita, Sootra Sthana, 17:69; P 351). In this stage the disease becomes incurable and this proves the hereditary and genetic predisposition nature of diabetic retinopathy.

When *Avarana samprapti* is continued for longer period, it will attain *dhatu kshaya avasta* and *dhatukshayaja samprapti* will continue in further stages of disease process. Again due to *Dhatwagnimandya* improperly formed *Rasa dhatu* in inadequate form is released, which leads to successive *Anulomajanya Dhatu kshaya*. Here *Dhatu kshaya* indicates the *sookshma/poshak dhatu* not the *sthoolarupidhatu*. Four internal patalas of eye are based on functional part of *sookshma* and *asthayeedhatus*. The manifestations of the diseases depend on the affected dosha, dhatu and srotas. These *sookshma rupi dhatus* of *Dristipatala* in eyes gets affected easily by the vitiated *doshas* due to either *Avarana* or *dhatukshyajanya samprapti* alone or by combination of both. Probable correlation of *dhatu kshaya* symptoms and pathogenesis of Diabetic Retinopathy is depicted in Fig. A.3.

2.3. Ama dosha and diabetic retinopathy

Agnimandya at the gastric level (*Jatharagni*) and at the tissue level is well established in *Prameha* and *Madhumeha* in Ayurveda. And in *Raktaja vyadhi*, *Agnisada* is another feature according to Charak (Tripathy Brahmananda, 1999, Caraka Samhita, Sootra Sthana, 24:13; P 430) and *Rakta* is one of the *dushya* in *madhumeha*. *Dhatwagnimandya* leads to accumulation of *Ama* at the tissue level. This can be correlated with generation of reactive oxygen species (ROS), activation of polyol pathway and accumulation of Advanced Glycation End products (AGEs), which are the main pathways of development of retinopathy in diabetics. Both *Charak* and *Sarangadhar* have mentioned very profoundly about *Dhatumalas* and all these can be corroborated to *dhatwagnimandya* related *malavriddhi*. In the context of *dhatusneha parmpara* in *Grahanichikitsa*, *Charak* has described the *Prasadabhaga*, which nourishes the successive *dhatu* and *Kittabhaga*, which nourishes the three humors of the body *Vata*, *Pitta* and *Kapha*. But in *Dhatwagimandya* state, the quantities of *Malarupi dosha* are increased and create the pathological features inside the body. *Mala* of *Rasa dhatu* and *Rakta dhatu* are *Kapha* and *Pitta* respectively (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 15:18; P 554). This *malarupi pitta* can create Diabetic Retinopathy pathology in the presence of *pitta* predisposing factors in retina. Relation between *Agnimandya*, *Ama dosha* and Oxidative stress pathogenesis of Diabetic Retinopathy is depicted in Fig. A.4.

2.4. Ojas kshaya and diabetic retinopathy

Madhumeha is also known as *Ojameha*. The vitiated dosha obstructed the path of Vata and vata carried the *Ojas* to the basti

and causes *madhumeha* (Tripathy Brahmananda, 1999, Caraka Samhita, Sootra Sthana, 17:78–81; P 355). According to *Chakrapani apara Oja kshaya* occurs in *madhumeha* and the seat of Apara Oja are ten *Mahamula dhamanis*. Loss of *Oja* leads to loss of *dhamanis* as per *ashrayaashrayeesambandha*. This can be correlated with loss of capillaries and thus due to *Ojakshyaya* abnormal apoptosis can enhance, leads to loss of capillaries and basement membrane thickening. Among the functions of Oja are *bahya* and *avyantara karana* (indriya) *karma*, means motor and sensory functions. Sushruta also mentioned *abhighata*, *soka* (grief), *kshaya* (*dhatukshya*), *kopa* (anger) as causes of *Ojas kshaya* (Trikamji J, Ram N, 2012, Susruta Samhita Dalhana Commentary, Sootra Sthana, 15:23–26; P 72). In case of diabetes along with *dhatu kshaya*, psychological stress is another factor which plays important role in *oja kshaya*. Loss or diminution of sensory functions including visual loss which are prominent features *oja kshaya*.

2.5. Prameha and diabetic retinopathy

Among 20 *pramehas*, 19 pramehas except *Madhumeha* are almost having renal and urinary pathology. Main pathological features of *prameha* are: *Pravuta avilamutrata* means increase in quantity of turbid urine in patients with prameha. Proteinuria can be correlated with *pravuta avilamutrata* [11]. As in long run; *prameha* is converted to *madhumeha* stage, this nephropathy signs are mostly associated with chronic cases of diabetes. Proteinuria leads to hypoalbuminemia and this decreases serum osmolarity [12], which again leads to salt and water retention in extracellular space of retina. This may be another cause of diabetic macular edema and retinal edema in general.

3. Visual symptoms of *timir* and diabetic retinopathy

Diabetic Retinopathy can be compared to *Timira* involving all the four *patalas*. Patalas are described on the basis of functional composition of *dhtaus* of *dristi*. The symptoms of vision are manifested when the vitiated *dosha* afflicting the concerned *dhatu* in *dristi patalas*. All the three *dosha* in single or in combination can affect one or more *patalas* of *dristipatala* (Retina). On the basis of different symptoms of *Timira* and stages of Diabetic retinopathy, a probable correlation and classification of Diabetic retinopathy is depicted in Table A.2.

4. Management of diabetic retinopathy in Ayurveda

Treatment is all about correcting and preventing the etiopathological mechanism (*Samprapti vighatana*). So as per etiopathological mechanisms described above, the first and foremost care should be given to prevent *madhumeha*. The treatment of diabetic retinopathy revolves around treating the causes of *madhumeha*, management of Urdwaga *Raktapitta*, treatment of *Avarana*, prevention of *dhatu kshaya* including *oja kshaya* and prevention of *Agnimandya* in general.

4.1. Agni chikitsa

Eye is not different from the body. So when we treat eye ailments it's necessary to treat the body at cellular level. *Agnimandya* at tissue level is called *Dhatwagnimandya*. With proper dipana pachana drugs, like *Trikatu churna*, *Jatharagni* as well as *Dhatwagni* can be corrected as per individual requirement.

4.2. Srotas sodhan chikitsa

Sodhan chikitsa are important part of all the *Ayurvedic* therapies. Due to *dhatwagnimandya*, accumulation of impurities occurs at the *srotas*/capillary level. For this *Virechan* can be advocated. *Nasya* with oil prepared from *chakshyusya* drugs should be done for *urdhwajatrugata srotas sodhan*.

4.3. Raktapitta Samak Chikitsa

Treatment of *Raktapitta* and *Raktaja vyadhi* are similar as per charak. These are *Raktapittahari kriya*, *virechan*, *Upavasa* (fasting) and *Raktamokshana* (Tripathy Brahmananda, 1999, Caraka Samhita, Sootra Sthana, 24:18; P 431). As Bloodletting is contraindicated in case of *Timir*, except *Raktamokshana*, all the procedures should be advised in case of different stages of *Madhumehajanya timir*. Even *Yogratnakar* and *Chakradutta* have mentioned *Langhana* (fasting) as *Sadpachanani* for treatment of eye diseases in general. As in diabetic retinopathy main *dosha* involved are *Vata and Pitta* along with *Kapha anubandha*, the *Pitta* should be treated first, as the aggravated *dosha* becomes more powerful in its own functional seat/place (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 28:188; P 971).

4.4. Avarana chikitsa

The *Avarana* should be treated by measures which are *Anabhisyandi* (non obstructive), *Snigdha* (unctuous) and *Srotosudhikar* (purifier of channels). Depending on the strength of the patient, *Yapana Basti* and *mrudu samsodhan* therapy can be given. All the palliative and preventive *Rasayan* drugs are useful for the prevention and treatment of *Avritta* induced disorders. Especially *Shilajatu*, *Guggulu*, *Chyavanprash* and *Brahma rasayan* are mostly helpful (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 28:240–242; P 981). These *Rasayan* drugs are also useful in diabetic retinopathy cases, as oxidative stress theory is well established in pathology of Diabetic Retinopathy and *Ama* theory in *madhumeha* too has role in development of Diabetic Retinopathy. *Eranda Taila* is beneficial in almost all the *Avarana* and works as *Sramsana*. *Yapana Basti*, Yasthimadu Ksheera Basti, Panchatikta Pancha Prasritika Basti and Guduchyadi Ksheera Basti may be administered in Pitta and Rakta Avarana [13].

4.5. Dhatu kshaya Chikitsa

As *dha tukshaya* leads to all vascular changes in diabetic retinopathy. *Madhumeha* is *vata dosha* predominant and is considered as *asadhya* (incurable) because of *maha atyayatwat* (due to chronic depletion of successive *dhatu*). Thus *Charak* has mentioned *Paritarpan* (nourishing therapy) after purification therapy for diabetic patients. *Even Timir* is included under *Vataja nanattmaja vyadhi*, so *Timir* can be treated with *Santarpan chikitsa* after proper purification therapy. So *Basti* treatment may be administered for *madhumehajanya timir*, as *Basti* therapy does both *sodhana* and *shaman*.

4.6. Vatanuloman chikitsa

Virechan and *Basti* with *chakshyushya* drugs should be advocated to control *Vata*. *Sothahar* (anti-inflammatory) treatment can be instituted with *Basti* treatment to reduce retinal/macular edema in general. In this context *Madutailika Chakshyusya Basti* (Gupta Atridev, 2008, Ashtanga Hridaya, Kalpasthan, 4:27–28; P 600) may be administered in Diabetic macular edema (DME) cases, as this *Basti* is beneficial in *Rakapitta* as well as *chakshyusya* in nature.

4.7. Urdwa jatrugata chikitsa

Nasya, *Shirodhara*, *Shirolepa* and *Shiropichu* treatments can be given in different stages of diabetic retinopathy on the principle of "*Vata shaman* treatment for head and body, and *pitta Shaman* treatment for eyes" (Santhakumari P.K, 2009, P 231).

4.8. Kriya kalpa and management of diabetic retinopathy

Kriya kalpa is an integral part of ayurvedic ocular therapeutics. *Pariserka*, *Aschyotan*, *Tarpan* and *Putapaka* can be given after proper evaluation of indications and contraindications.

4.8.1. Tarpana

Tarpana procedure in posterior segment diseases of eye like DR is of great importance as most of the drug permeation to intraocular tissues occurs through the cornea to the aqueous humor and ciliary vessels. As retinal pigment epithelium is continued as the non pigment epithelium of ciliary body, the drugs get absorbed through cornea may reach to the inner 3/4th retinal layers and outer 1/4th layers of retina gets from choroidal vessels from systemic route. Pre corneal drug retention, tissue contact time, molecular weight and size of the drug, lipophilicity of medicine affects the amount of drug permeation through the cornea. In Tarpan procedure the medicated Ghritas are administered and kept in eyes for 15–20 min. Drug availability in intraocular tissues increases due to longer duration of drug contact and, lipophilic and hydrophilic nature of drugs in medicated ghritas in *Tarpana* procedure. Lipophilic drugs are better permeated through epithelium and endothelium and hydrophilic drugs are better penetrated through the stromal layer of cornea. In case of different stages of DR the medicines like Patoladi ghrita, Jivantyadi ghrita, Drakshyadi ghrita can be used in Tarpan procedure to alleviate hemorrhagic signs due to raktapitta samak, ropaka and rasayana properties of these drugs. Doorvadya ghrita Tarpana is effective in mild to severe NPDR and PDR (Raktapitta janya) cases [14]. Mahatriphala Ghrita (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:13–15; P 671) can be used for Tarpana in PDR cases as neovascularisation is a pathological feature in PDR (Pranavritta vyana janya) and Triphala has anti VEGF properties [15] in eyes owes to reduce symptoms in PDR cases. In retinal ischemic conditions of DR due to Dhatukshyajanya pathology Jivantyadi Grita Tarpana (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:2–3; P 670) and in leucocyte activated increased blood viscosity due to Raktavritta Vata janya cases Patoladi ghrita Tarpana (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:7–9; P 671) can be advised.

4.8.2. Putapaka

Putapaka is similar to Tarpana in procedure of administration but methods of preparation of drug differ. This preparation contains herbomineral drugs processed with ghee, meat and fats of animal origin and subjected to heating in a furnace. This liberates nanoparticles of drug in ionized form which easily penetrates into cornea due to ionized and lipophilic nature of the drug and reaches the posterior segment tissues of the eye in a similar pathway like Tarpana procedure. As the drugs are in minute form and due to vyavayi and vikashi guna of drugs owes to addition of agni during preparation, the drug reaches the inner retinal layers. Ropana type of putapaka is indicated in Pitta, Rakta, Vrana conditions of eye and thereby Ropana Putapaka can be used in different stages of DR. Breast milk, meat of animals of Jangala origin, honey, ghee and Tikta rasa herbal drugs are used for Ropana Putapaka [16]. Putapaka prepared from Tikta dravya like Vasa can be used after Tarpana karma for optimum therapeutic effect in different stages of DR cases.

4.8.3. Pariseka/Seka

Seka is done as *Poorvakarma* before *Tarpana*. This helps in vasodilatation of superficial vessels and some amount of medicines get absorbed through the medial canthus which is highly vascularised. *Ropana* type of *Seka* is indicated in *Rakta* and *Pitta* diseases of eye. Thus *Ropana* type of *Seka* advised in DR helps in improving texture of blood vessels, endothelial repair and thereby prevents loss of the pericytes, which is an initial factor in DR development. *Pariseka* with drugs having *Tikta Kashaya Rasa* and *Chakshyusya* properties helps in healing intra retinal blood vessels and arrests bleeding due to *Sthambhana* properties. This might prevent vascular endothelial growth factor (VEGF) activation, which is primarily responsible for retinal neovascularisation in PDR cases. Triphaladi Pariseka [17] Manjisthadi Pariseka (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 16:13; P 686), Chandanadi Pariseka and Vasakadi kwatha Pariseka (Sastri Lakshmipati, 2013, Yogaratnakara, Netraroga Chkitsa, P 388) will helpful in reducing *Raktapitta* pathology in different stages of DR pathology.

4.8.4. Aschyotana

Aschyotana is the technique of introducing small volume of drug in open eye repeatedly. The medicines introduced in the form of medicated decoction are absorbed through the blood vessels of fornices of conjunctiva, sclera and highly vascularized part of inner canthus. Therapeutic actions of Aschyotana are like Seka procedure. The drops which are lipid base in the form of medicated Ghee preparations permeates through the cornea due to both lipophilic and hydrophilic drug molecules in the medicated ghee preparations. Medicines like Triphaladi ghrita, Doorvadi ghrita and Patoladi ghrita can be used as Aschyotanain the dose of 3–4 drops in mild to moderate DR cases. Triphaladi [17], Prapoundarikadi (Sastri Lakshmipati, 2013, Yogaratnakara, Netraroga Chkitsa, P 391) and Manjisthadi (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 16:13; P 686) Aschyotana can be used in initial stages of NPDR cases.

4.8.5. Anjana

Anjana is a medicinal preparation which is applied on the lower palpebral conjunctiva or the cul-de-sac. Drug permeability to intraocular tissue depends on their hydrophilicity and lipophilicity mainly occurs through the conjunctiva and cornea by paracellular and transcellular pathways respectively. pH, viscosity, tonicity, molecular size and molecular weight of the active ingredients are factors responsible for the therapeutic effect of Anjana. According to its form *Anjana* is of 3 types i.e. *Gutika*, *Rasakriya* and *Churna*. *Gutika* and *Churna* types of *Anjana* can be correlated with ophthalmic suspensions and *Rasakriya* type is with aqueous solutions/eye drops. *Gutika* and *Churna Anjana* have micro particles which may be deposited in the cul-de-sac and increases the pre corneal retention time and thereby increases the drug bioavailability to intraocular tissues. Due to large molecular size both the trans-sclera and trans-corneal drug absorption may occur in Anjana procedure. Ropana and Dristiprasadana type of Anjanas might be helpful in treating and preventing DR pathogenesis in pakwavastha. Sarivadyanjana (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:65; P 676) and Drakshyadi varti anjana (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:74; P 677) described by Vagbhatta in Pittaja and Raktaja Timir chikitsa respectively may help in hemorrhagic

stages of DR pathology. Sriparnyadi anjana [17] described by Yogratnakar in the context of Raktabhisyanda can be advised in different stages of DR pathology.

4.9. Chakshyusya/Netrya Basti

Though Basti is considered as the best treatment for Vata Dosha it is advised even for the treatment of Pitta Dosha, Kapha Dosha and Sarvadhatu AshritaVyadhi (Trikamji J, Ram N, 2012, Susruta Samhita Dalhana Commentary, Chikitsa sthana, 35:6; P 525). Sushruta described both Timir and Adhimantha are among eye diseases which can be treated with Basti Chikitsa (Trikamji J, Ram N, 2012, Susruta Samhita Dalhana Commentary, Chiki tsasthana, 35:5; P 525). While describing the importance of Basti Chikitsa, Acharya Sushruta has mentioned "Chakshyuhu Prinayati", which means improves vision. While describing treatment of Timir, Vagbhatta mentioned Basti as one of the treatment procedure along with Murdhabasti, Tarpana, Alepana etc. Again he had mentioned Niruha and Anuvasana Basti procedure for VatajaTimir (Gupta Atridev, 2008, Ashtanga Hridaya, Uttarasthana, 13:47, 62; P 674–675). *Chakshushya Basti* [18] is especially mentioned by Vagbhatta for its Chakshyusya, Pramehahara and Raktapittahara properties. This is a type of Siddhabasti and contains ingredients of *Madhutailika Basti* (*Erandmoola Kwath*, *Madhu*, *Taila*, *ShatpushpaKalka* and *Saindhavlavana*) with *Yastimadhu Kalka. Yogvahi, Raktapittahar* and *Sandhan* properties of *Madhu* helps in better absorption of the drugs and healing effect on intra retinal blood vessels. *Sukshma and Tiksna Guna* of *Saindhav* helps in reaching up to micro channels and break down of morbid Dosha. *Chakshushya* effect of Saindhava lavana attributed to temporary osmotic BRB disruption for better enhancement of drug absorption in Basti procedure. *Taila* is best drug for *Vata dosha* alleviation. *Vyavayi*, *Ushna*, *Guru* and *Snighda* properties of *Taila* pacifies *Vata dosha* and improves drug permeability of cell membrane. Rasayana, chakshyusya and ropana properties of Yasthimadhu help in repair and regeneration of intra retinal blood capillaries. *Shatpushpa* increases the retention time of *Basti* and has Akshirogahara properties. *Vrishya* and *Vatahar* properties of Erandamoola Kashaya help in pacifying *Vata,* regeneration of retinal capillaries and provide nutrition to retinal ganglion cells. Other Chakshyusya Basti formulations like Sthiradi Niruha Basti (Tripathy Brahmananda, 1999, Caraka Samhita, Siddhi Sthana, 3:36–37; P 1204) and Mustadi Yapana Basti can be advised in different stages of DR. Panchatikta Pancha prasritika Basti (Tripathy Brahmananda, 1999, Caraka Samhita, Chikitsa Sthana, 8:8; P 1261) can be advised in initial stages of active Sirabhisyanda and diabetic retinopathy patients having predominant in kleda and kapha vitiation i.e., NPDR due to retinal ischemia. In case of Dhatukshya stages of DR, Sthiradi Niruha Basti can be administered, which has nutritive effect on retinal neuronal layers. The rationale behind use of Basti in posterior segment diseases of eye including DR is to introduce large volume of drugs through systemic route. Drug ionization through proper emulsification, lipophilicity, and molecular weight, pH and transit time of drugs are the factors which influences drug absorption and bioavailability to the ocular tissues. Basti treatment meets all these properties along with unique anatomical characteristic of a large surface area which can deliver enormous drug to posterior segment of eye for effective therapeutic effect in the ocular conditions. Pathogenesis of major diseases of posterior segment of eye is caused by *Sira Srotas Abhisyanda* due to *doshaavarana*, *dhatuksyaya* with resultant reduction of supply of nutrients to the ocular tissues. Basti does both *Sodhana* and *Shamana* along with enhancement of nutritional status of dhatus in the body which also applies to the *dhatus* or *Patalas* in Eye. Stimulation of autonomic nervous system could be the possible mechanism behind action of Basti. There is a close resemblance in the functioning of Vata Dosha and nervous system and Basti is prescribed as the best remedy for *Vata*. It again validates the efficacy of Basti karma on nervous system as well as in ocular disorders. There is a close resemblance between pharmacological actions of Basti, with colon specific drug delivery system (CSDDS) [19] and strategies required for CNS drug delivery [20]. Methods such as prodrug, carrier mediated drug delivery, drug manipulation by lipophilic analogs and osmotic blood brain barrier disruption or blood retinal barrier disruption strategies described by modern pharmacologists, completely compliments with classical methods of Basti procedure. The rectal columns have a rich vascular bed and have their own arteries and veins. While the superior rectal vein drains via the inferior mesenteric vein into the portal vein, the inferior and middle rectal veins drain directly into the inferior vena cava via the internal pudendal vein and the internal iliac vein. This type of vascular supply of rectum helps in achievement of systemic drug effect.

4.10. Oral systemic drugs

Triphaladi churna, Triphaladi kwatha, Mahavasadi kwatha [14], Vasakadi kwatha and Amrutadiguggulu [21] can be advised in mild to severe NPDR and PDR cases.

5. Conclusion

Diabetic retinopathy is a disease of *Dristipatala* (retina) and complication of long standing uncontrolled diabetes due to defective metabolism and endocrine dysfunction. All the three *doshas* are affected with *rakta* (as both *dosha* and *dushya*), mainly *vata*, *pitta*, *rakta* and *kapha anubandha*. All the *dhatus* are affected with *rakta, meda* and *mamsa* predominant, *sira srotas* of *raktavaha srotas* and *Ojavaha dhamani* gets affected in successive stages. If the DR pathology is analyzed properly, it possesses all the four features of *srotovaigunya i.e.*, *Atipravritti, Sanga, Siragranthi and Vimarga gamana. Sanga* is manifested by the retinal vessels occlusion leading to hypoxic related ischemia. *Siragranthi* is nothing other than development of microaneurysms, *Vimarga gamana* is the retinal haemorrhages and *Atipravritti* can be correlated to the Neovascularization where new vessels are formed. *Agnimandya* and *Ama* formation, *raktapitta, avarana* and *dhatu kshaya* are few aspects of pathogenesis and development of Diabetic retinopathy and this may provide inputs for development of treatment protocol for the disease in Ayurveda in future.

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Conflict of interest

None declared.

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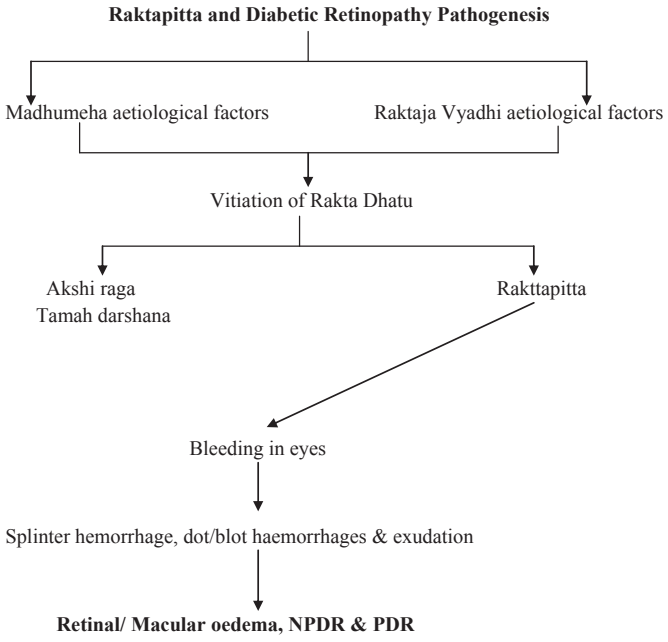

Fig. A.1. *Raktapitta* and diabetic retinopathy pathogenesis.

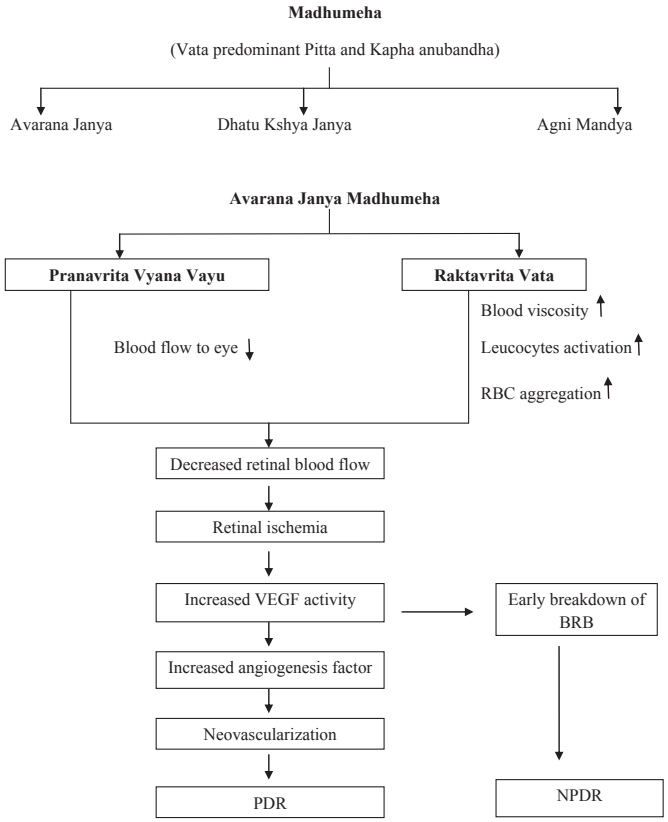

Fig. A.2. Avaranajanya *Madhumeha Samprapti* and pathogenesis of diabetic retinopathy.

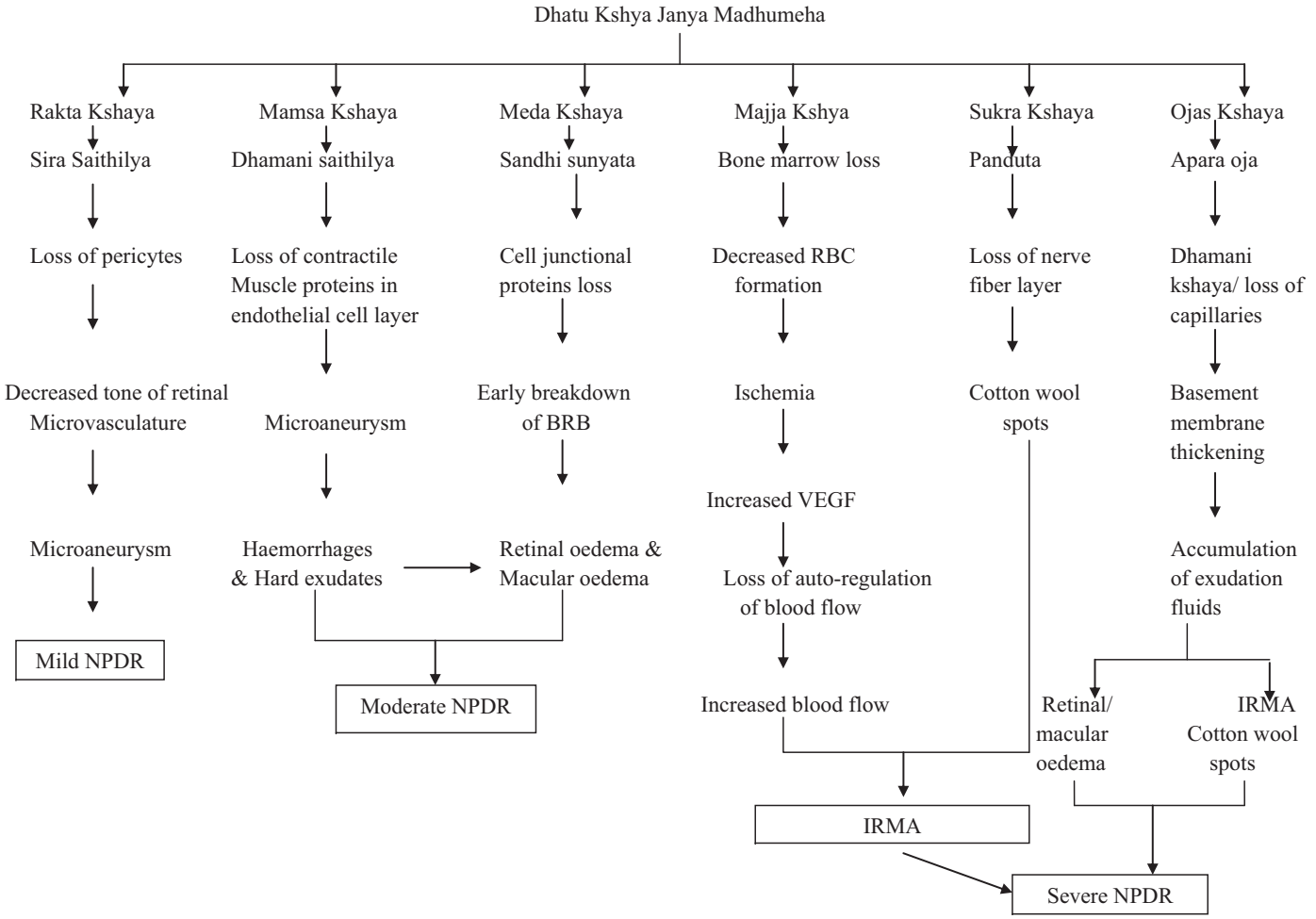

Fig. A.3. Dhatu kshaya symptoms and pathogenesis of diabetic retinopathy.

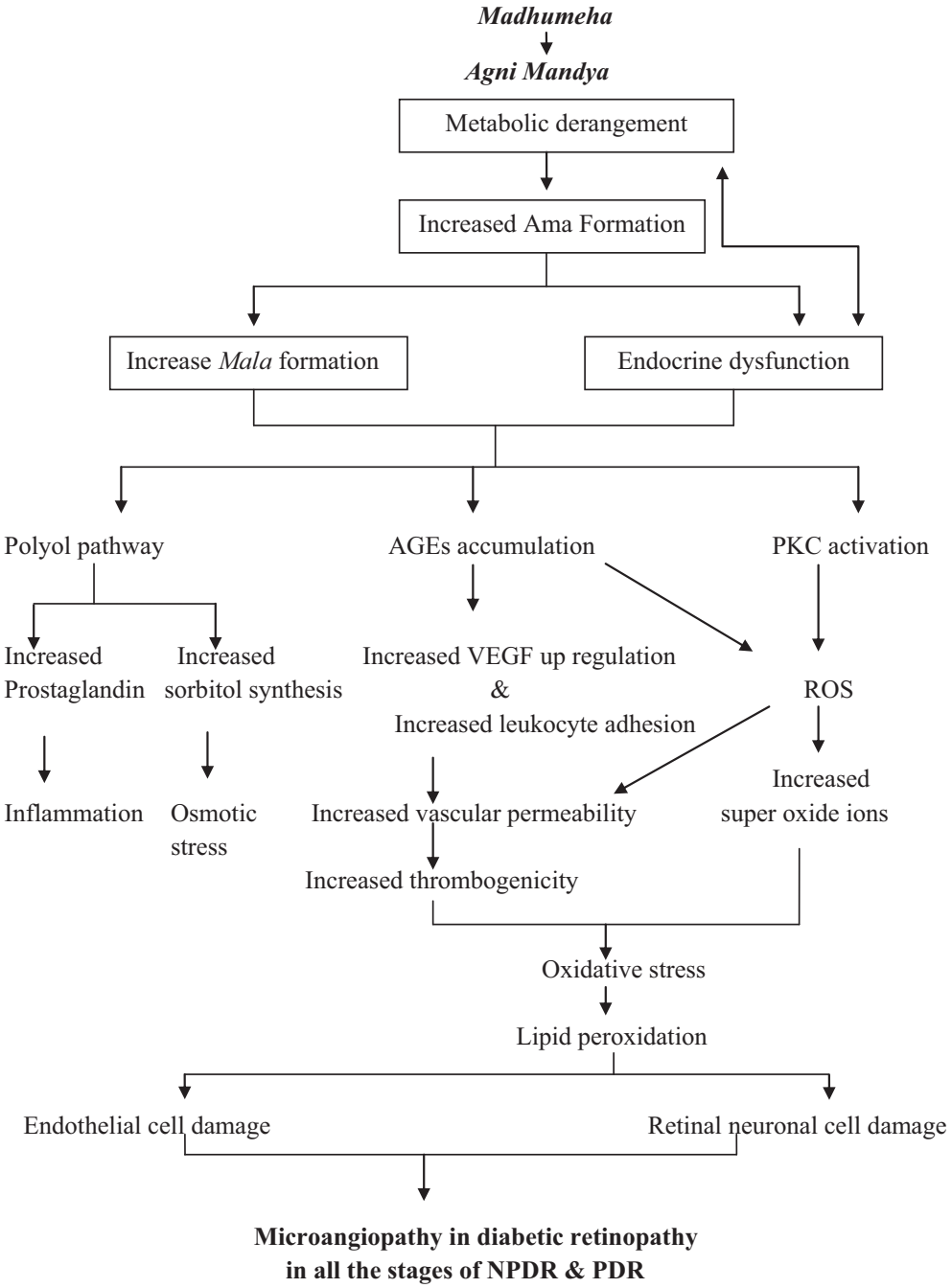

Fig. A.4. *Agnimandya*, *Amadosha* and oxidative stress pathogenesis of diabetic retinopathy.

Table A.1
Probable correlation of *Dhatu Kshaya* symptoms and vis-à-vis diabetic retinopathy symptoms.

Dosha: Vata Pitta pradhan, initiated by *kapha* (*kapha anubanhda*)		
Dushya:	*Kshaya lakshyana*	Interpretation of diabetic retinopathy symptoms
Meda (Surplus and unutilized fat or adipose tissue)	*Sandhisunyata*	Cell junction or adhesion defect/Break down of blood retinal barrier. Macular edema and Exudates formation.
Mamsa (Muscular tissue/muscle protein)	*Dhamanisaithilya*	Loss of junctional adhesion molecule/endothelial cell loss.
Rakta (Blood)	*Sirasaithilya*	Loss of pericytes, weakening of capillary walls and formation of microaneurysms.
Majja (Marrow tissue)	*Timiradarshana*	↓blood cell formation – anemia – hypoxia – breakdown of BRB – loss of nerve fibers – cotton wool spots.
Sukra (Semen)	*Panduta*	Proves hereditary and genetic predisposition of Diabetic retinopathy.
Ojas (Resistance factor/Immunity)	*Vyathitendriya*	Diminish in function of sense organs including blurred in vision.

Table A.2
Probable correlation of *doshaja timir* vis-à-vis different stage of Diabetic retinopathy [22].

Patalas	*Doshaja timir*	Visual symptoms	Modern correlation/classification of DR
Ist (*Teja Jalashrita*)	*Vataja*	Blurring of vision, Erythropsia, Micropsia Metamorphosia	Mild NPDR
	Pittaja	Color vision defects	
IInd (*Mamsashrita*)	*Raktaja*	Blackouts/Scotomas Smoky vision Color vision defects	Moderate NPDR
	Sannipataja	Polyopia, Diplopia Visual field defects Photopsia	Severe NPDR Preproliferative PDR
IIIrd (*Medashrita*)	*Parimlayee Timir* (*Pitta* + *Rakta*)	Photopsia Phosphenes	PDR Vitreos hemorrhages Retinal detachment
	Parimlayee Kacha	*Ragaprapta* *Dosha Dhatu Kshaya* Snow flake cataract	Diabetic Cataract
IVth (*Asthyashrita*)	*Sannipatika Linganasha*	Loss of vision	High Risk PDR Florid PDR

NPDR–Non proliferative Diabetic Retinopathy, PDR–Proliferative Diabetic Retinopathy.

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