Eur J Nutr (2017) 56:2013–2027
DOI 10.1007/s00394-017-1406-2

REVIEW

Nutrition for diabetic retinopathy: plummeting the inevitable threat of diabetic vision loss

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Received: 24 June 2016 / Accepted: 10 February 2017 / Published online: 3 March 2017

Abstract Diabetic retinopathy (DR) is among the leading causes of preventable blindness. Hyperglycemia, hypertension, hyperlipidemia and anemia majorly predispose its pathogenesis. The current treatment modalities of DR include laser photocoagulation therapy, intravitreal corticosteroids, intravitreal anti-vascular endothelial growth factor (VEGF) agents and vitreo-retinal surgery which are costly, highly invasive, unproven for prolonged use and opted in advanced stages of DR. By then retina already encounters a vast damage. Nutrients by their natural physiological, biochemical and molecular action can preserve retinal structure and functions by interfering with the various pathological steps prompting DR incidence, thereby altering the risk of developing this ocular morbidity. Nutrients can also play a central role in DR patients resistant towards the conventional medical treatments. However due to the byzantine interplay existing between nutrients and DR, the worth of nutrition in curbing this vision-threatening ocular morbidity remains silent. This review highlights how nutrients can halt DR development. A nutritional therapy, if adopted in the initial stages, can provide superior-efficacy over the current treatment modalities and can be a complementary, inexpensive, readily available, anodyne option to the clinically unmet requirement for preventing DR. Assessment of nutritional status is presently considered relevant in various clinical conditions except DR. Body Mass Index (BMI) conferred inconclusive results in DR subjects. Subjective Global Assessment (SGA) of nutritional status has recently furnished relevant association with DR status. By integrating nutritional strategies, the risk of developing DR can be reduced substantially. This review summarizes the subsisting knowledge on nutrition, potentially beneficial for preventing DR and sustaining good vision among diabetic subjects.

Keywords Diabetic retinopathy · Nutrients · Nutritional status · Body Mass Index · Subjective Global Assessment

Introduction

Diabetic retinopathy (DR) is among the leading causes of preventable blindness worldwide [1]. It is a microangiopathy, majorly caused by hyperglycemia, hypertension, hyperlipidemia and anemia which through a series of pathological processes, contribute to the pathogenesis of DR [2–4]. The current treatment modalities of DR include laser photocoagulation therapy which is intrinsically harsh, suffering with unavoidable side effects of visual field loss and is not completely successful in reversing or arresting vision loss [5]. Intravitreal corticosteroids involve side effects such as infection, glaucoma and cataract formation [6]. Intravitreal anti-vascular endothelial growth factor (VEGF) agents administration is an invasive procedure, ensuing with the risk of endophthalmitis, retinal detachment along with the probability of imparting deleterious effects on the remaining healthy retina and can cause systemic complications as they can gorge into the systemic circulation which can

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be hazardous for diabetic patients with expected long-term administration [7]. Vitreo-retinal surgery is an expensive procedure, requiring experienced vitreoretinal specialists and is opted in advanced stages of DR [8]. By that time retina already encounters a vast damage. A wide array of nutrients, by their natural physiological, biochemical and molecular action, can preserve retinal structure and functions by interfering with the various pathological steps prompting DR incidence, thereby altering the risk of developing this ocular morbidity. Nutrients can also play a central role in DR patients resistant towards the conventional medical treatments. Recently nutrition-based approaches have gained momentum in various clinical conditions. As DR is a nutritionally responsive disorder, the defensive role of nutrition in daunting DR deserves spotlight. But probably due to the byzantine interplay existing between nutrients and DR, the worth of nutrition in curbing this vision-threatening disorder remains silent. A nutritional therapy, if adopted in the initial stages, can be an anodyne option proving effective, inexpensive and readily available in halting DR onset or progression. Nutrition-based approaches can provide superior efficacy and propose a complementary solution to the clinically-unmet requirement for preventing DR. This review is an effort to summarize the subsisting information on nutrition which can be applied for arresting the pathogenesis of DR and sustaining good vision among diabetic subjects.

Clinical manifestations of diabetic retinopathy

Clinically DR can be classified as Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) [9–11]. Non-Proliferative Diabetic Retinopathy is characterized by basement membrane hypertrophy, loss of pericytes and formation of microaneurysms. Pericyte loss causes development of microaneurysms, retinal vascular hyperpermeability and impaired blood-retina barrier resulting in diabetic macular edema and spillage of plasma lipoproteins, leading to formation of retinal hard exudates. Loss of pericyte also leads to capillary acellularity precipitating retinal ischemia. Retinal ischemia is among the primary angiogenic stimulus responsible for the ischemia-driven angiogenic pathology. Non-Proliferative Diabetic Retinopathy is also marked by inflammation which results in increased activation of leukocytes with elevated levels of inflammatory cytokines and adhesion molecules; leading to increased capillary stasis, occlusion and ultimately hypoxia [9, 10]. Hypoxia stimulates development and proliferation of new vessels which in due course, cause pathological vasoproliferation initiating PDR (Fig. 1)

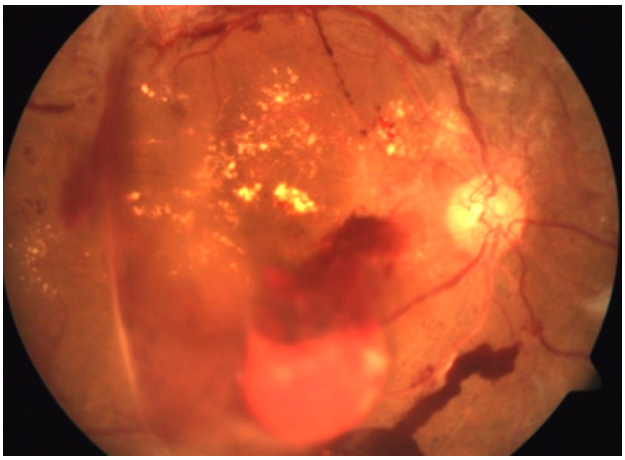


Fig. 1 Color fundus photograph showing microaneurysms, hard exudates, hemorrhages and proliferative new vessels in proliferative diabetic retinopathy

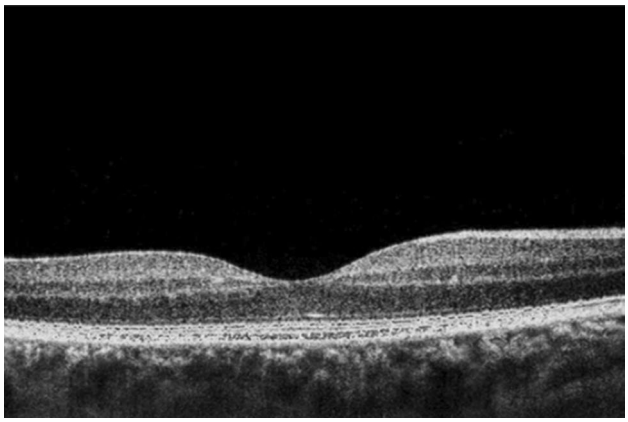


Fig. 2 Spectral domain optical coherence tomography showing normal macula

which may trigger contraction of the vitreous and fibrovascular proliferation thereby triggering retinal distortion and tractional detachment. Vision loss occurring at this stage is mainly caused by macular ischemia, chronic macular edema (Figs. 2, 3) and macular detachment [11]. Hyperglycemia and diabetes-induced metabolic changes alters the vitreous gel and vitreoretinal interface. Collagen fibril cross-linking and accumulation of advanced glycation end products (AGEs) augment vitreoretinal adhesion, incite retinal glial cell reactivity and alter concentration of various soluble proteins. Vitreous gel is an important regulator of intraocular oxygen tension having important implications in DR which is also precipitated by retinal hypoxia [10, 11].

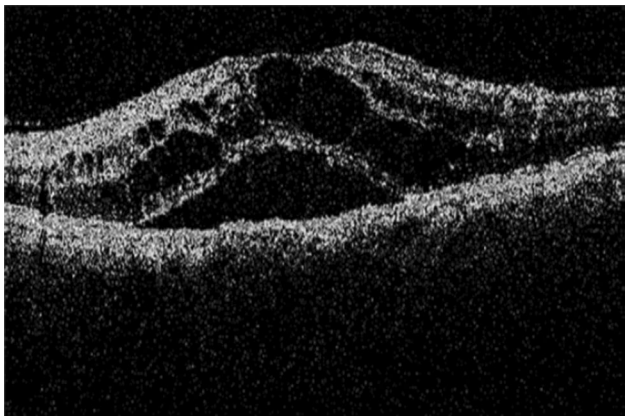


Fig. 3 Spectral domain optical coherence tomography showing diabetic macular edema

Processes involved in pathogenesis of diabetic retinopathy

Hyperglycemia, hypertension and hyperlipidemia majorly cause decreased visual acuity or vision loss via certain pathological processes.

Aldose reductase pathway

Elevated intracellular glucose levels cause increased activation of the aldose reductase pathway which is also known as the polyol pathway or the sorbitol pathway. It results in decline of intracellular nicotinamide adenine dinucleotide phosphate (NADP) that reduces the production of nitric oxide (NO) in endothelial cells (ECs). This pathway also leads to chronic galactosemia causing vascular basement membrane changes, pericyte loss, development of microaneurysms and capillary acellularity. Excessive amount of galactose competes with glucose for the glucose transporters (GLUTs), thereby limiting the entry of glucose in retinal cells and diminishing glucose-requiring cellular energy metabolism [9].

Advanced Glycation End products (AGEs)

Formation of AGEs directly damage cells by impairing the function proteins, i.e., extracellular proteins like collagen and the intracellular proteins. The cellular effect of AGEs is mediated by its binding to AGE-receptors which initiates a cascade of signal transduction involving p21ras, p44/p42 mitogen activated protein kinase (MAPK), nuclear factor-κB (NF-κB) and protein kinase C (PKC). Activation of these intracellular kinases subsequently leads to cell dysfunction [9].

Reactive oxygen intermediates

Chronic hyperglycemia also increases oxidative stress. Free radicals such as superoxide anions are produced as byproducts of oxidative phosphorylation of glucose and by glucose autoxidation. High glucose levels increase their production causing oxidative stress. Oxidative stress reduces NO levels, promotes leukocyte adhesion to the endothelium, decreases barrier function of ECs, damages cellular proteins and activate PKC by increasing the formation of diacylglycerol. Free radicals can damage mitochondrial DNA (mtDNA) and cellular proteins [9].

Protein Kinase C (PKC)

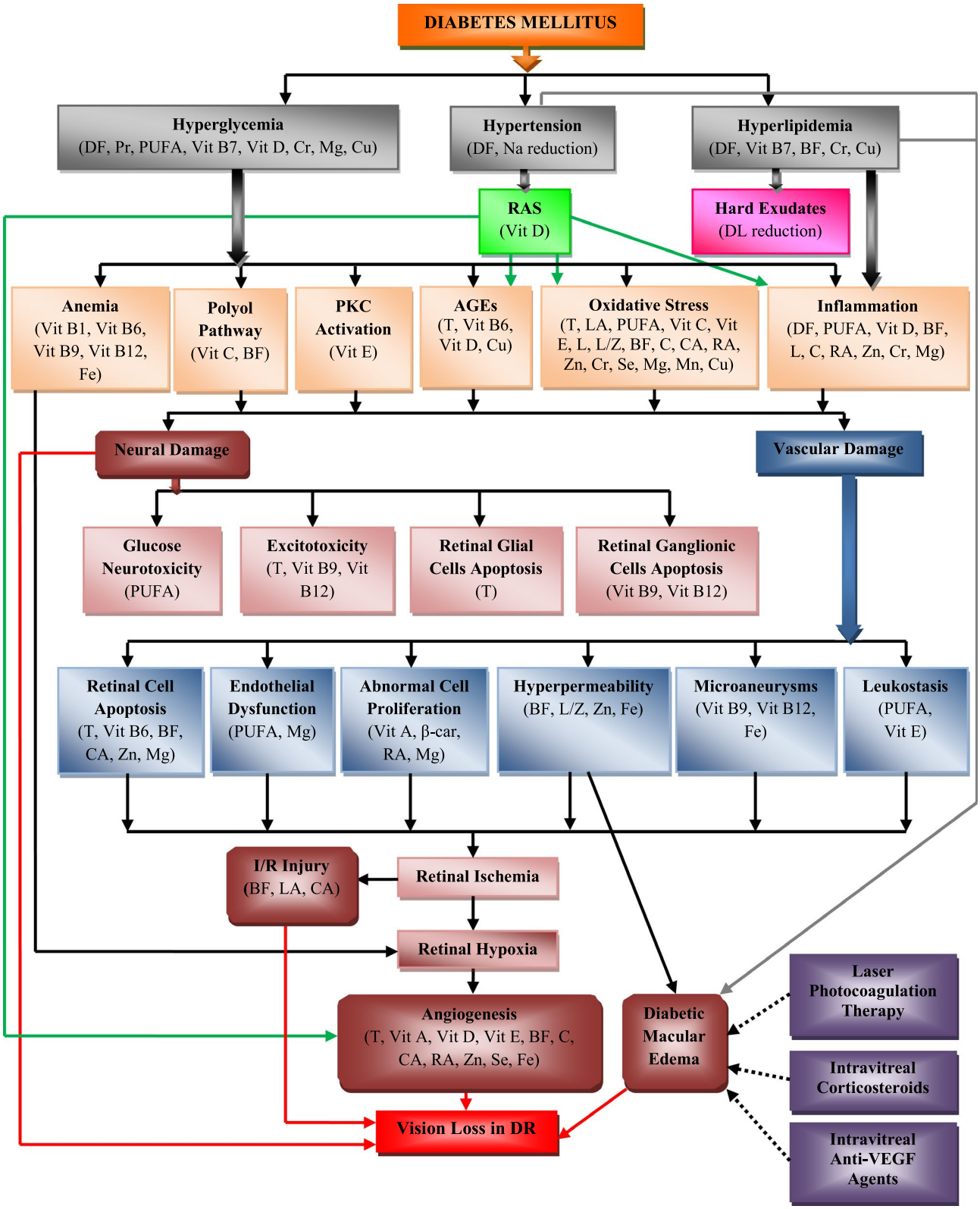
Hyperglycemia can result in pathological activation of PKC. Protein Kinase C is a ubiquitous enzyme, capable of promoting vascular damage by increased vascular permeability, disruption of NO regulation, increased leukocyte adhesion to vessel walls and changes in blood flow without the involvement of the aldose reductase pathway. Protein Kinase C activation can influence MAPK or NF-κB pathways [9].

Renin–Angiotensin system(RAS)

Apart from hyperglycemia, RAS is another potential angiogenic mechanism participating in DR incidence. It induces microvascular complications such as vasoconstriction, inflammation, oxidative stress, cell hypertrophy and proliferation, angiogenesis and fibrosis [12]. Renin, an angiotensin-converting enzyme, and angiotensin II receptors are present in retinal and choroidal vessels and angiotensin acts as an angiogenic growth factor stimulating formation of new retinal blood vessels, by upregulating VEGF activity and other growth factors such as platelet-derived growth factor and connective tissue growth factor and also increases exudation from retinal vessels [13, 14].

Hyperlipidemia

Hyperlipidemia increases blood viscosity and alters fibrinolytic system causing hard exudates formation [15]. Hard exudates are lipoprotein deposits that are often associated with macular edema [16]. Apart from retinal thickening, the severity of retinal hard exudates is a significant risk factor for moderate visual loss and decreased visual acuity [17].


DIABETES MELLITUS
Hyperglycemia (DF, Pr, PUFA, Vit B7, Vit D, Cr, Mg, Cu)
Hypertension (DF, Na reduction)
Hyperlipidemia (DF, Vit B7, BF, Cr, Cu)
RAS (Vit D)
Hard Exudates (DL reduction)
Anemia (Vit B1, Vit B6, Vit B9, Vit B12, Fe)
Polyol Pathway (Vit C, BF)
PKC Activation (Vit E)
AGEs (T, Vit B6, Vit D, Cu)
Oxidative Stress (T, LA, PUFA, Vit C, Vit E, L, L/Z, BF, C, CA, RA, Zn, Cr, Se, Mg, Mn, Cu)
Inflammation (DF, PUFA, Vit D, BF, L, C, RA, Zn, Cr, Mg)
Neural Damage
Vascular Damage
Glucose Neurotoxicity (PUFA)
Excitotoxicity (T, Vit B9, Vit B12)
Retinal Glial Cells Apoptosis (T)
Retinal Ganglionic Cells Apoptosis (Vit B9, Vit B12)
Retinal Cell Apoptosis (T, Vit B6, BF, CA, Zn, Mg)
Endothelial Dysfunction (PUFA, Mg)
Abnormal Cell Proliferation (Vit A, β-car, RA, Mg)
Hyperpermeability (BF, L/Z, Zn, Fe)
Microaneurysms (Vit B9, Vit B12, Fe)
Leukostasis (PUFA, Vit E)
I/R Injury (BF, LA, CA)
Retinal Ischemia
Retinal Hypoxia
Angiogenesis (T, Vit A, Vit D, Vit E, BF, C, CA, RA, Zn, Se, Fe)
Diabetic Macular Edema
Laser Photocoagulation Therapy
Intravitreal Corticosteroids
Intravitreal Anti-VEGF Agents
Vision Loss in DR

◂**Fig. 4** Schematic representation showing various nutrients potential in halting the pathogenesis of diabetic retinopathy on earlier steps as compared to the contemporary treatment modalities (laser photocoagulation therapy, intravitreal corticosteroids and intravitreal anti-VEGF agents) which are indicated at the stage of diabetic macular edema. *β-car* β carotene, *BF* Bioflavonoids, *C* Curcuminoids, *CA* Caffeic acid, *Cr* Chromium, *Cu* Copper, *DF* Dietary fibres, *DL* Dietary lipids, *DR* Diabetic retinopathy, *Fe* Iron, *I/R* Ischemia Reperfusion, *LA* α-lipoic acid, *L* Lycopene, *L/Z* Lutein/Zeaxanthin, *Mg* Magnesium, *Mn* Manganese, *Na* Sodium, *Pr* Protein, *PUFA* Polyunsaturated fatty acids, *RA* Rosmarinic acid, *RAS* Renin Angiotensin System, *Se* Selenium, *T* Taurine, *VEGF* Vascular endothelial growth factor, *Vit A* Vitamin A, *Vit B1* Vitamin B1, *Vit B6* Vitamin B6 , *Vit B9* Vitamin B9, *Vit B12* Vitamin B12, *Vit C* Vitamin C, *Vit D* Vitamin D, *Vit E* Vitamin E, *Zn* Zinc

Nutrients and diabetic retinopathy

Nutrients can interfere with the discussed pathological processes, impeding the development and progression of DR (Fig. 4). Majority of the beneficial nutrients can be included in the diet of diabetic subjects through various foods rich in these nutrients (Table 1). Hence, the role of these nutrients in terms of this ocular morbidity needs to be highlighted.

Carbohydrates

Carbohydrate intake was found associated with the severity of DR and consequent deterioration of visual acuity [18–20]. Carbohydrates when ingested in the form of sucrose, break down into glucose and fructose. Fructose was found responsible for retinal changes. Metabolism of fructose in diabetic retina lead to the formation of lactate which acts as a pathogenic agent in retinopathy development [18]. Fructose-rich diet also increased AGE formation [21].

Dietary fiber

Diabetic patients are advised a low carbohydrate diet recommending at least half of the daily energy intake to be derived from fiber-rich complex carbohydrates [22]. High-glycemic index foods on ingestion induce higher blood glucose concentration and chronically increased insulin demand leading to pancreatic exhaustion thereby resulting in glucose intolerance [23]. Dietary fibers lead to quicker intestinal transit by lessening carbohydrate absorption time in upper jejunum and decrease the insulin demand [24]. Dietary fibers slowed glucose response after ingestion, improved diabetic dyslipidemia, suppressed low-grade systemic inflammation and lowered blood pressure [25, 26]. Dietary fiber intake correlated with the progression and severity of DR [27].

Protein

Although, higher protein intake did not improve DR status [19, 20], it ameliorated glycemic control and hyperglycemia in diabetics and pre-diabetics without any pharmacological intervention [28, 29].

Amino acid 'taurine'

Taurine is present in very high concentrations in the retina [30]. Dietary taurine supplementation ameliorated DR by normalizing retinal vascular function and attenuating induction of retinal VEGF which is associated with neovascularization [31]. Taurine lowered VEGF levels present in retinal homogenates by reducing oxidative stress [32]. Diffusion of nutrients from the vasculature is prevented in diabetes by AGE deposition along with developing a hypoxic environment for retinal pigment epithelium and photoreceptors. Taurine treatment reduced a high-fructose diet-induced AGE formation [33]. It attenuated glial fibrillary acid protein (GFAP) induction, which is a marker of gliosis and apoptosis in retinal glial cells in diabetes and also decreased retinal carbonyl dienes significantly [31]. Taurine supplementation ameliorated DR by anti-excitotoxicity of glutamate and declined glutamate levels, intermediate filament GFAP, N-methyl-D-aspartate receptor subunit 1 expression and gamma aminobutyric acid levels and it also increased glutamate transporter expression in diabetic retina [34].

Lipids

Hyperlipidemia increases blood viscosity and alters fibrinolytic system causing hard exudates formation [15]. Hard exudates accumulation at the center of the macula deteriorates visual acuity [17]. Elevated lipids caused hypoxia, increased LDL oxidation, release of cytokines and growth factors and endothelial dysfunction (ED). Endothelial dysfunction in diabetic vasculature leads to breakdown of blood–retinal barrier [15]. Lipids exudate through damaged retinal vasculature, causing diabetic macular edema [16]. Retinal hemorrhage and edema also occurs due to triglycerides incorporation into cell membranes causing alteration in membrane fluidity leading to plasma constituent leakage in the retina [15]. Small low-density lipoprotein (LDL) particles easily cross the endothelium and are readily oxidized. Oxidized LDL has prothrombotic effect which is mediated by PKC activation. It is toxic to pericytes and ECs of the retinal capillary contributing to retinal capillary injury. Very low-density lipoprotein (VLDL) increases plasminogen activator inhibitor-1 secretion by ECs. High-density lipoprotein is found to have a protective role against retinopathy due to its paraoxonase activity which detoxifies the

Table 1 List of nutrients and their related food sources

Nutrients	Food sources
Dietary fiber	Whole grains, bran (oat, wheat, rice, corn), green leafy vegetables, cauliflower, broccoli, cabbage, beans, peas, pumpkin, mushrooms
Protein	Fish (cod, tuna, salmon), low fat cheese, skimmed milk, yoghurt, soymilk, tofu, tempeh, egg white, lean turkey, chicken breast, almonds
Taurine	Sea food, shellfish, dark meat of chicken, fish (salmon, tuna, sardines), cheese, yoghurt, milk, eggs, oatmeal, wheat germ
High-Density Lipoproteins (HDL)	Plant oils (olive, flaxseed, canola), soybeans, legumes, whole grains, fish (salmon, tuna, sardines), almonds, avocados
α-Lipoic acid	Spinach, broccoli, tomatoes, green peas, Brussels sprouts, rice bran
Poly-Unsaturated Fatty Acids (PUFA)	Plant oils (olive, canola, flaxseed), walnuts, fish (sardines, tuna, salmon), cod liver oil, tofu, soybeans, Brussels sprouts, broccoli, cauliflower
Vitamins	
Vitamin A	Carrots, green leafy vegetables, pumpkin, squash, lettuce, fish (tuna, mackerel), oysters, papaya, prunes, peaches
Vitamin B6 (Pyridoxamine)	Spinach, avocados, apricots, seeds (sunflower, flax, sesame), fish (tuna, salmon, herring), turkey, chicken
Vitamin B7 (Biotin)	Peas, cauliflower, lentils, oatmeal, barley, rice bran, avocados, sunflower seeds, peanuts, walnuts
Vitamin B9 (Folic acid)	Green leafy vegetables, broccoli, cauliflower, celery, peas, Brussels sprouts, carrots, squash, citrus fruits, beans, lentils, avocado
Vitamin B12 (Cobalamine)	Shellfish, crustaceans, fish (mackerel, salmon, tuna, herring, sardine), tofu, soymilk, eggs, skimmed milk, yoghurt, Swiss cheese, fortified cereals
Vitamin C	Citrus fruits, guava, berries, kiwifruit, tomatoes, green leafy vegetables, cauliflower, broccoli, red and green cabbage, Brussels sprouts
Vitamin D	Cod liver oil, fish (salmon, herring, tuna, mackerel, sardine), mushroom, tofu, soy yoghurt, eggs, vitamin D fortified cereals and dairy products, almond milk
Vitamin E	Green leafy vegetables, almonds, seeds (sesame, sunflower), pumpkin, squash avocado, shellfish, fish (salmon, herring), plant oils (olive, wheat germ, canola)
Carotenoids	
β-Carotene	Carrot, green leafy vegetables, lettuce, squash, pumpkin, broccoli, peas, peaches, prunes, apricot
Lycopene	Tomatoes, carrot, asparagus, red cabbage, guava, papaya, grapefruit
Lutein/zeaxanthin	Green leafy vegetables, lettuce, broccoli, Brussels sprouts, peas, leeks, green beans, squash, basil
Bioflavonoids	Berries, cherries, citrus fruits, papaya, grape fruit, green and red vegetables, green tea, garlic, parsley, peppermint, thyme
Curcuminoids	Turmeric
Caffeic acid	Apples, berries, pears, cinnamon, cumin, ginger, nutmeg
Rosmarinic acid	Thyme, peppermint, sage, oregano
Minerals	
Zinc	Spinach, beans, squash, pumpkin, wheat germ, mushroom, chicken, oyster, almonds
Chromium	Broccoli, green beans, basil, apples, oranges, garlic, turkey
Selenium	Brazil nuts, mushroom, lima beans, brown rice, broccoli, cabbage, spinach, whole grain, seeds (chia, flax, sesame), seafood, fish (tuna, halibut, sardine), eggs
Magnesium	Green leafy vegetables, squash, pumpkin, beans, lentils, almonds, tuna fish, low fat cheese, yoghurt, milk, whole grains, avocado
Manganese	Seafood, almonds, seeds (chia, sesame, flax), whole grain, tofu, tempeh, beans, green leafy vegetables, black tea
Copper	Mushroom, beans, green leafy vegetables, goat cheese, tempeh, avocado, seeds (chia, sesame, flax), nuts, seafood
Iron	Pumpkin, squash, green leafy vegetables, peas, whole grains, lentils, chickpeas, tofu, almonds, chicken liver
Sodium (to be avoided)	Baking powder, cured meat and fish, pickles, salted nuts, chips, French fries, canned vegetables, sauces, excessive table salt

lipid peroxidation products [35]. Previous studies reported elevated lipid levels as an important contributing factor in the pathogenesis of DR [15, 16, 35]. Alteration and reduction in dietary lipid intake in order to sequentially reduce serum lipids for halting the pathogenesis of DR has been proposed by previous studies [36, 37].

Fatty acids

α-Lipoic acid

It is an organosulphur compound derived from octanoic acid which is an eight carbon saturated fatty acid [38]. α-Lipoic acid is a biological antioxidant with reactive oxygen species (ROS) scavenging potentials [39]. It inhibited the development of DR by preventing accumulation of oxidatively modified DNA, diabetes-induced increase in nitrotyrosine levels and decrease in retinal mitochondrial and cytosolic ratios of oxidized and reduced nicotinamide adenine dinucleotide (NAD + and NADH) and also prevented activation of NF-κB and decreased VEGF levels and oxidatively modified proteins in retina [40, 41]. It protected retina against ischemia–reperfusion injury which is one of the major cause of vision loss in DR [42].

Poly Unsaturated Fatty Acids (PUFAs)

Poly unsaturated fatty acids can inhibit the development and progression of DR [18, 22, 43–45]. Poly unsaturated fatty acids metabolites i.e., lipoxins, resolvins and protectins exhibited anti-inflammatory action by suppressing interleukin (IL)-6, tumor necrosis factor (TNF)-α, VEGF and ROS and also restored antioxidant homeostasis. Production of brain-derived neurotrophic factor is augmented by PUFA which can protect retinal neuronal cells from degeneration caused by DR [45]. Poly unsaturated fatty acids according to their chemical structure can be classified into two groups which are ω-3 and ω-6 fatty acids [46]. Linoleic acid, an ω-6 fatty acid and α-linoleic acid, an ω-3 fatty acid are essential fatty acids required to be supplemented through diet. ω-3 and ω-6 essential fatty acids are metabolized into longer chain PUFAs by elongase and desaturase enzymes [47]. Linoleic acid is metabolized to arachidonic acid and α-linoleic acid to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Retina is rich in arachidonic acid, EPA and DHA [45]. Neurons need a steady glucose supply and neuronal glucose uptake depends on extracellular glucose concentration. Diabetes-induced persistent hyperglycemia leads to glucose neurotoxicity. ω-3 PUFAs improved glucose tolerance and preserved retinal functions in diabetes [44]. Compromised endothelial progenitor cells lead to inadequate vascular repair in DR. Acid sphingomyelinase participates in dysfunction of endothelial progenitor cells (EPCs) and initial retinal damage. A DHA-rich diet inhibited acid sphingomyelinase in both, EPCs and retina thereby correcting EPCs number and function, preventing diabetes-induced retinal vascular pathology and suppressing retinal inflammation [43]. Poly unsaturated fatty acids, especially EPA and DHA prevented IL-6 and TNF-α production and suppressed intercellular cell adhesion molecule-1 and vascular cell adhesion molecule expression and VEGF secretion. High-glucose-induced retinal vascular endothelial damage is prevented by linoleic acid and arachidonic acid [45].

Vitamins

Vitamin A

Vitamin A or retinol protected retina from hyperglycemia-induced retinal hazards in diabetes as it is required for normal cell growth and its deficiency can initiate retinal changes like cell proliferation in DR [48]. It retarded neovascularization and retinal pigment epithelium cell proliferation [49]. Previous study confirmed relationship between vitamin A deficiency and DR occurrence [48].

Vitamin B

Association of B vitamins and DR have been reported by previous studies [50, 51]. Hyperglycemia in diabetic milieu promotes vascular superoxide production, sequentially inactivating NO expression by ECs leading to vascular degeneration. B vitamins enhance NO production and are specifically essential in maintaining the overall vascular system integrity [50]. Pyridoxamine or vitamin B6 inhibited late stages of glycation reactions that cause AGE formation, thus being capable of protecting against premature pericyte cell death temporally maintaining capillary viability. It also inhibited acellular strand formation in diabetic retina thereby maintaining microvascular cellularity [52]. Biotin or vitamin B7 supplementation improved glucose management by enhancing glucose uptake in skeletal muscle cells and increasing glucose disposal. It was also found potential in improving lipid metabolism [53]. A low concentration folic acid or vitamin B9 and cobalamine or vitamin B12 increased the risk of vascular damage by homocysteine [51]. It hinders retinal arterioles dilation through NO-mediated pathway and induces apoptosis in retinal ganglion cells by increasing expression of Bcl-2-associated X protein, a pro-apoptotic protein expression, found in increased levels in diabetic retinas [50, 54, 55]. Homocysteine, if incorporates with proteins by a disulphide or amide linkage, it causes significant oxidative stress and inflammation [50]. It also disrupts glutamate homeostasis by acting as an agonist at the glutamate site of N-Methyl-D-Aspartate

receptors [56, 57]. High homocysteine levels are toxic to pericytes and EC lining of the walls of retinal blood vessels causing vascular thrombosis and microaneurysms [50]. Homocysteine is detoxified by methionine synthetase, which depends on vitamin B9 and B12 as coenzymes for its proper functioning [58]. Dietary deficiency of folic acid and cobalamine causes hyperhomocysteinemia [51]. Supplementation of vitamin B9 and B12 reduced homocysteine levels [59].

Vitamin C

Development of DR may be prevented by vitamin C intake as it is a chain-breaking antioxidant, scavenging ROS directly, preventing breakdown of NO and decreasing LDL oxidation [60]. It reduces platelet aggregation, affects retinal blood flow and acts as an aldose reductase inhibitor of the hyperglycemia-induced polyol pathway [61–63]. It protects against detrimental effects of high oxidative stress occurring due to non-enzymatic glycosylation, auto-oxidative glycosylation and metabolic stress among diabetics [64]. Previous studies reported lower vitamin C levels in DR patients compared to the ones without retinopathy [65, 66].

Vitamin D

Vitamin D is a potent inhibitor of angiogenesis and its anti-angiogenic effect may be mediated by vitamin D receptor present in the retina [67]. Vitamin D suppressed RAS, creating anti-inflammatory and immune-suppressive effect [68, 69]. It decreased VEGF, replication of vascular smooth muscle cells and cytokine production by downregulating NF-κB and increasing IL10 thus reducing inflammation. It reduced negative effect of AGEs on ECs and inhibited production and activity of tissue matrix metalloproteinases that induce thrombosis. Vitamin D is required for efficient insulin secretion and insulin functioning [70]. Insulin-like growth factor-1 was found associated with DR [71]. Active forms of vitamin D regulate several insulin-like growth factor binding protein genes [72]. Prior studies reported association of vitamin D with DR [70].

Vitamin E

Vitamin E is present in retina predominantly in the form of α-tocopherol [73]. The role of vitamin E in preventing DR owes to its free radical scavenger activity outside the cells by non-enzymatic mechanism [74]. It can normalize diabetic retinal hemodynamics and reduce production of VEGF and overproduction of intercellular cell adhesion molecule-1 [75]. It inhibited hyperglycemia-induced diacylglycerol PKC pathway in retinal tissues that caused decrease in retinal blood flow promoting retinopathy [74, 76]. Thus, vitamin E can prevent pathogenesis of DR.

Carotenoids

Carotenoids can be discriminated into pro-vitamin A and non pro-vitamin A carotenoids. β-carotene is the only pro-vitamin A carotenoid present in the ocular tissue. The non-pro-vitamin A carotenoids present in the ocular tissue in high concentrations are lycopene and lutein/zeaxanthin [77].

β-carotene

β-carotene, due to its antioxidant properties, protected retina from the active free radicals rendered degeneration [78]. It can protect against hyperglycemia hazards like initiation of cell proliferation involved in DR [48].

Lycopene

It is the most potent singlet oxygen quencher carotenoid. It modulated lipoxygenase activity and in turn inflammation and immune function. It increased antioxidant activity in ocular capillaries [77]. Significantly lower serum lycopene levels were observed in patients with advanced stages of DR [79].

Lutein/zeaxanthin

They are isomers of each other and the only carotenoids present in the retina. They have antioxidant effect and improved visual acuity. They inhibited free radicals combining with retinal collagen, strengthened retinal collagen structure, reduced vascular permeability and leakage and maintained blood vessel integrity [80]. They can reduce the risk of DR pathogenesis [77, 80].

Bioflavonoids

Bioflavonoids exhibit antioxidant activity by scavenging free radicals directly; inhibiting enzymes responsible for superoxide production and chelating ROS enhancer trace elements. They improved ocular blood flow, decreased angiogenesis and vascular leakage, inhibited aldose reductase activity and also exhibited anti-inflammatory activity [81]. They also prevented neuronal degeneration in inner retina resulting from ischemic injury [82]. The usual source of bioflavonoids are pulp and rinds of fruits and vegetables. They are also present in green tea which can be beneficial in controlling DR when recommended as nutritional supplements [83, 84].

Green tea

Green tea or Camellia sinensis is a rich source of catechins whose antioxidant activity is many times higher than vitamin C and E. Green tea suppressed hyperlipidemia, reduced plasma hydroperoxides, ameliorated retinal superoxide formation and also normalized erythrocyte glutathione [83]. Green tea prevented angiogenesis by inhibiting hypoxia-inducible factor-1 alpha protein expression and sequentially turned down VEGF expression [85]. Green tea also reduced anion production level and restored glutamate transporter, glutamate receptor and glutamine synthetase thereby maintaining retinal functions equivalent to non-diabetics. It inhibited acellular capillaries, pericyte ghost formation and ameliorated structural lesions in DR [84].

Curcuminoids

They are turmeric constituents. Curcumin, which is one of the curcuminoids, prevented diabetes-induced decrease in total antioxidant capacity of retina [86]. It inhibited accumulation of 8-hydroxyl-2′ deoxyguanosine in diabetic retina [87]. The anti-inflammatory action of curcumin targets anti-inflammatory biomarkers such as 5-hydroxy-eicosatetraenoic acid, cyclooxygenase and lipoxygenase [88, 89]. Dietary supplementation of curcumin prevented IL-1β, VEGF, TNF-α and diabetes-induced NF-κB activation [86, 87]. The anti-angiogenic activity of curcumin includes decrease in stromal cell-derived factor-1-induced migration of human retinal ECs, VEGF-induced PKC-β II translocation and inhibition of increased VEGF levels in retina [86, 90, 91]. Oral administration of curcumin inhibited increase of retinal acetylated histones that were noticed in the development of DR [92].

Caffeic acid

It demonstrated antioxidant and potential anti-angiogenic activity on retinal ECs and retinal neovascularization respectively by suppressing ROS-induced VEGF expression. It effectively inhibited VEGF-induced retinal EC proliferation and VEGF-induced migration and tube formation of retinal ECs [93]. Caffeic Acid Phenethyl Esters, a caffeic acid derivative protected retina from ischemia/reperfusion injury by enhancing antioxidation ability and preventing retinal cell apoptosis [94]. It inhibited lipid peroxidation in retina by scavenging peroxy radicals, reduced NO overproduction and nitrosative stress and regulated superoxide dismutase enzyme activity in diabetic retina [95].

Rosmarinic acid

It exhibited anti-inflammatory and antioxidant properties [96]. It decreased intracellular ROS levels, IL-8 release and VEGF expression [97]. It also showed anti-angiogenic activity to retinal neovascularization and inhibited retinal EC proliferation and angiogenesis [98].

Minerals

Zinc

It is present in retina in high concentrations and can protect retina from ROS-induced pericyte apoptosis [99]. Zinc acted as an antioxidant as it halted free radicals formation by inhibiting NADPH oxidase [100]. It is essential in copper–zinc superoxide dismutase formation which is required for maintaining erythrocyte antioxidant defense enzymes, preventing diabetes-induced plasma malondialdehyde increase, protecting retina against diabetes-induced increase in lipid peroxidation by binding and stabilizing cell membranes thus preventing their disintegration by inducing metallothioneins production [101, 102]. Zinc can prevent neovascularization by inhibiting VEGF expression and inflammatory cytokine production by suppressing NF-κB activation. It prevented vascular leakage in DR [99].

Chromium

Chromium deficiency led to elevated blood glucose levels [103]. Since retina is a high energy-demanding tissue, glucose uptake, regulation and utilization is required for maintaining normal retinal functions [104]. Glucose transporter proteins, GLUT-1 and GLUT-3, transport glucose across the blood–retinal barrier in the retina [105, 106]. In DR, GLUT-1 and GLUT-3 expression is reduced. Chromium histidinate, a chromium compound, increased GLUT-1 and GLUT-3 expression for compensating the retinal glucose need [107]. Retina being rich in polyunsaturated lipid membranes is very sensitive to ROS that cause lipid peroxidation. Retinal oxidative stress is induced by hyperglycemia [108]. Trivalent chromium supplementation can reduce cellular oxidative stress and blood levels of pro-inflammatory cytokines and lipids [109]. Chromium supplements can improve retinal functions as well as blurred vision [103, 110, 111]. Dietary chromium supplementation suppressed diabetes-induced retinal tissue damage [108].

Selenium

It is one of the major non-enzymatic antioxidants of the body [112]. Selenium prevented the hazards of DR by downregulating VEGF production, ameliorating

diabetes-induced biochemical retinal abnormalities and protecting cells against oxidative damage caused by peroxides generated from lipid metabolism [113–115]. It protected from oxidative stress by modulating cellular response and inhibiting ROS production. Glutathione peroxidase, a very important antioxidant, catalyzing decomposition of ROS, is a selenium-dependent enzyme. Selenium deficiency exacerbates oxidative stress in diabetes. It complements vitamin E functioning against oxidative stress by affecting the absorption and biological activity of vitamin E and preventing its decomposition [116].

Magnesium

Hypomagnesemia is a risk factor in DR development [117]. Magnesium deficiency induced pro-inflammatory and profibrogenic response and also oxidative stress due to reduction of certain protective enzymes [118–120]. Magnesium deficiency can interfere with the normal cell growth and apoptosis regulation as it plays an important role in DNA synthesis and repair [121]. Low magnesium levels caused microvascular complications by inhibiting procyclin receptor function creating imbalance between prostacyclin and thromboxane effect [122]. As magnesium is a physiological calcium antagonist, its low levels can cause vascular calcification and increased platelet aggregation promoting EC dysfunction and thrombogenesis [123, 124]. Increase in peripheral intracellular free calcium concentration also inhibited insulin action on glucose uptake further worsening hyperglycemia [123]. Magnesium also acts as a cofactor of the glucose transport mechanism in the cell membranes and aids carbohydrate oxidation enzymes, insulin secretion, binding and activity [125]. Oral magnesium supplementation improved insulin sensitivity and metabolic control in diabetic subjects with low serum magnesium levels [126].

Manganese

Manganese in the form of manganese superoxide dismutase inhibited oxidative stress and prevented DR development [127]. Diabetes cause dysfunctional retinal mitochondria, decrease in reduced glutathione levels, apoptosis of retinal capillary cells and lesions in retinal ECs. Manganese superoxide dismutase overexpression protects mitochondrial encoded genes and inhibited mtDNA damage preventing the plausible mechanism of DR pathogenesis [128].

Copper

It is an essential dietary micronutrient. Its deficiency caused altered glucose metabolism, hypercholesterolemia, compromised oxidant defense system, increased diabetes-induced glycation, peroxidation and nitration. Copper deficiency led to decreased activity of oxidant defense enzyme copper-zinc superoxide dismutase and selenium-dependent glutathione peroxidase and altered ROS scavengers like glutathione and metallothioneins altering oxidant defense system causing excessive oxidative stress and tissue damage [129]. But hyperglycemia induces fragmentation of copper-containing enzymes like ceruloplasmin and copper–zinc superoxide dismutase releasing copper ions in the blood [130]. Free copper participates in Fenton and Haber–Weiss reactions generating ROS, thus behaving as a potential cytotoxic element by increasing oxidative stress and AGEs formation [131]. Previous studies reported raised serum copper levels with the presence and increasing severity of DR [130, 132].

Iron

Iron deficiency caused by nutritional anemia precipitates DR. Treating nutritional anemia by iron, vitamin B1, B6, B9 and B12 supplements led to spontaneous closure of microaneurysms, reduced superficial hemorrhages and cotton-wool spots and improved visual acuity [133]. Anemia induced retinal hypoxia [134]. Treating anemia increased tissue oxygenation and reduced VEGF production which further halted the stimulus for neovascularization and improved hyperpermeability [135]. One-third of anemia occurs due to nutrient deficiency including iron deficiency, either alone or together with folate or vitamin B12 deficiency [136]. Iron deficiency anemia rapidly led to PDR pathogenesis [3]. Hyperglycemia completely destroys heme molecules of hemoglobin and myoglobin, releasing free iron. Free iron is a highly pro-oxidant molecule capable of generating powerful ROS and stimulates expression of monocyte endothelial adhesion and adhesion molecules which leads to pathogenesis of DR. Free iron catalyzes binding of AGEs to specific receptors and regulates L-glutamate production which is involved in retinal neurodegeneration [137]. As these activities lead to the pathogenesis of DR, maintaining iron homeostasis is essential.

Sodium

Macular edema, a leading cause of visual impairment in DR was found associated with sodium intake. Lowering sodium intake reduced blood pressure. Hypertension is among the risk factors of macular edema. Hence, high sodium intake was reported to be a risk factor in the progression of DR [138].

Nutritional status and diabetic retinopathy

Body Mass Index (BMI)

Many studies found an association between BMI and obesity with DR but the relationship between BMI and the associated risk of DR remained inconclusive [139–143]. This inconsistency could be due to the fact that BMI is deflected by the weight change of diabetic subjects. Diabetic retinopathy increases with uncontrolled diabetes which also causes unintentional weight loss and a low BMI. Hence, a low BMI can be associated with increasing severity of DR. Concurrently, obesity or a high BMI is often correlated with escalating grade of DR. This can be explained by the fact that obesity increases inflammatory markers. Adipose tissue secretes adipokines, such as IL-6, TNF-α, leptin and adiponectin. They regulate lipid levels, inflammation, oxidative stress, insulin resistance and diabetes occurrence [144] Obesity-associated oxidative stress and inflammation caused ED which leads to pathogenesis of DR. [145] Raised plasma leptin levels in obesity caused vascular EC proliferation, angiogenesis and neovascularization whereas; obesity associated low adiponectin levels led to insulin resistance [146, 147] Obesity also initiates hyperlipidemia and hypertension which are amongst the reckoned risk factors of DR.

Subjective Global Assessment (SGA)

Evaluation of nutritional status of DR subjects by BMI conferred ambiguous results. Subjective Global Assessment (SGA) is a consistent, dependable and reproducible clinical assessment method of nutritional status, based on the medical history and physical examination of the subject providing thorough estimation of the nutritional status as demonstrated by the previous studies in different clinical conditions [148, 149]. Subjective Global Assessment scores correlated with the presence and increasing severity of DR in our studies recently [150, 151]. Uncontrolled diabetes leads to increase in the grade of DR and is often accompanied by co-morbidities like diabetic gastropathy and nephropathy. These co-morbidities cause change in dietary intake, gastrointestinal disturbances, edema and weight fluctuations. Subjective Global Assessment scores are calculated after evaluating the overall health status of the subject than merely the anthropometric indices. Hence, SGA might overcome the ambiguities arising from BMI and may provide more discreet results for DR subjects.

Conclusion

In summary, nutritional strategies can substantially reduce the risk of developing DR, proving quite beneficial in DR cases resistant towards the conventional medical treatments. Nutritional treatment can preserve the normal physiology, structure and functions of retina. Nutrition-based approaches have a high potential to be developed as adjunct therapy for arresting the occurrence or progression of DR in early stages and can serve as a non-invasive and cost-effective treatment which can be within the means of every socioeconomic status. As the current treatment modalities are highly invasive, expensive and unproven for prolonged use due to their certain side effects, nutrition-based approaches can evolve as dependable, complementary therapies to the existing DR treatment inhibiting development of retinopathy and subsequent loss of vision in diabetic subjects.

Acknowledgements University Grants Commission, India (Funding Agency).

Compliance with ethical standards

Funding Junior Research Fellowship [No. F. 17-7/2011 (SA-I)] by the University Grants Commission, India.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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