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REVIEW

Diet, Mitochondrial Dysfunction, Vascular Endothelial Damage, and the Microbiome: Drivers of Ocular Degenerative and Inflammatory Diseases

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ABSTRACT

There is abundant evidence in medical literature that Western diet and lifestyle drive the cellular and metabolic processes which underlie chronic non-communicable diseases. However, non-pharmaceutical interventions, which focus on nutrition, the microbiome and lifestyle, to prevent non-communicable diseases are not part of mainstream treatment, for a variety of reasons. Lack of progress in stemming the rise in chronic non-communicable diseases can be attributed to the current 'downstream' medical paradigm which is focused on treating disease and symptoms, rather than preventing disease via an 'upstream' approach, which looks at cause and process. Metabolic abnormalities and obesity have previously been noted as correlated with common chronic ophthalmic conditions such as age related macular degeneration (AMD), glaucoma, ocular inflammation, diabetic retinopathy and retinal vascular occlusive disease. These are ocular manifestations of an underlying common cause. The aim of this paper, using an ophthalmic context, is to provide an overview of the cellular pathophysiological mechanisms that underlie chronic non-communicable diseases, including ophthalmic diseases, and to draw the links between diet and lifestyle, the microbiome and chronic non-communicable diseases.

Keywords: Diet; Mitochondria; Microbiome; Vascular endothelium; Glycocalyx; Lifestyle

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Key Summary Points

In the last 40 years a global epidemic of chronic non-communicable diseases has emerged, driven predominantly by overconsumption of ultraprocessed foods.

Excessive consumption of ultraprocessed foods results in cellular and metabolic processes that lead to obesity, mitochondrial dysfunction, insulin resistance, inflammation, vascular endothelial dysfunction and dysbiosis.

Obesity, mitochondrial dysfunction, insulin resistance, inflammation, vascular endothelial dysfunction and dysbiosis are unifying factors which underlie the majority of chronic non-communicable diseases.

Common chronic ophthalmic diseases, such as age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy, are the ophthalmic manifestations within the spectrum of chronic non-communicable diseases, sharing a common aetiology.

Greater awareness of the science underlying chronic non-communicable diseases creates an opportunity for improving outcomes in ophthalmic and systemic chronic non-communicable diseases.

INTRODUCTION

Since the early 1900's there has been an inexorable rise in chronic non-communicable diseases globally. In 1962 the prevalence of obesity in the USA was 13% [1, 2]. National Health and Nutrition Survey (NHANES) data from 2017–18 for the USA report a prevalence of overweight and obesity of 73.8%, with obesity being 42.8% [3]. Prevalence of metabolic syndrome (3 of abdominal obesity, hypertension, impaired fasting blood glucose, elevated serum triglycerides, low high density lipoprotein) in 2018 was 41.8% [4], with 82% of the population having at least one feature of metabolic syndrome, and up to 40% of people with a normal BMI (18–25 kg/m^2) being metabolically unhealthy [5].

Whereas in the late 1800's cardiovascular disease was virtually unrecorded, in 2019, 27% of deaths were caused by cardiovascular disease, making it the commonest cause of death globally. Other chronic diseases which have dramatically increased in prevalence, such as diabetes, stroke, cancer, neurodegenerative disease, inflammatory and autoimmune disease, and mental illness are all significant causes of mortality and morbidity. In the USA chronic non-communicable diseases affect 50% of people, account for 87% of deaths, and consume 85% of health budgets [6, 7]. It is estimated that 70–90% of these diseases are preventable by dietary and lifestyle modification [8].

In broad terms, the cellular pathophysiology of chronic non-communicable diseases, including the aforementioned ophthalmic diseases, can be attributed to mitochondrial dysfunction, inflammation, vascular endothelial dysfunction and activation of immune responses. These pathological processes are interdependent. There is a paucity in literature examining the correlation between diet, metabolic dysfunction, the microbiome and chronic ophthalmic diseases, and this paper provides an overview of the science. Topics discussed are:

1. the normal physiology of mitochondria and their role in controlling inflammation;
2. the vascular endothelium, with particular reference to the blood ocular barrier and the photoreceptor-retinal pigment epithelial complex;
3. the microbiome, it's role in regulating immune tolerance, and how dysbiosis is implicated in inflammation and autoimmunity;

Included will also be a review of the mechanisms by which Western diet and lifestyle disrupt mitochondrial function and cellular energetics, cause dysbiosis and drive systemic and ocular metabolic dysfunction, inflammation and autoimmune disease.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

EVOLUTION OF HUMAN DIET, WESTERN DIET, AND DIETARY COMPOSITION CHANGES

The evolution of the modern human diet began about 3 million years ago. The hominins of the time were scavengers (passive hunters), obtaining 60–70% of their nutrition from animal foods [9, 10]. About 1.5 million years ago hominins learned to control fire, allowing cooking of foods, the first example of food processing. This allowed more efficient extraction of nutrients and led to enlargement of the brain, and shortening of the gut [11]. Isolated indigenous hunter-gatherer societies still exist.

The agricultural revolution originated in the Middle East about 12,000 years ago, with the growing and processing of grains and other plant crops. The Ancient Egyptians ate a 'lacto-ovo-vegetarian' diet which was heavily wheat (bread) based. Statuary from the time demonstrates abdominal obesity in males and females, suggesting metabolic syndrome, as well as gynaecomastia in the males, evidence of excessive phytoestrogens contained in a plant based diet. Pathological studies of mummies from this civilisation reveal a high prevalence of extensive arterial atheroma at an early age, with early death being common. Literature from this period contains the first known description of the symptoms of myocardial infarction [10]. These studies are important, because they correlate a diet high in refined carbohydrate (bread), with metabolic syndrome and cardiovascular disease, in the absence of other known modern risk factors for these diseases, such as smoking, dietary seed oils and excessive added sugar.

The inexorable rise in chronic non-communicable diseases since 1980 is undeniable and alarming [12]. Comparison of Burden of disease data with dietary patterns from 1961–2021 shows that the biggest changes have occurred in the consumption of oils and fats, increased by 72%, sugar by 11%, cereals and grains by 24%, alcohol by 31%, meat by 43%, with other foods not significantly changed [12]. There is also evidence that 'obesogens' in food packaging and the environment contribute to altered energy balance signalling and epigenetic expression [13].

MITOCHONDRIA, THE VASCULAR ENDOTHELIUM, AND THE MICROBIOME IN THE PATHOPHYSIOLOGY OF INFLAMMATION AND CHRONIC NON-COMMUNICABLE DISEASE

Mitochondria

Mitochondria are considered to be bacteria which developed an intracellular symbiotic relationship with host eukaryotic cells approximately 1.5 billion years ago. They are motile, and dynamic, undergoing fission, fusion and multiplication, depending on metabolic stimuli (Fig. 1).

The matrix contains the mitochondrial DNA, and the enzymes which perform the oxidative phosphorylation of fatty acids and glucose, reducing nicotinamide adenine dinucleotide (NAD) to NADH, releasing electrons which enter the electron transfer chain on the inner membrane (complexes I–IV; Fig. 2).

As well as controlling cellular energetics mitochondria control regulated cell death (apoptosis), and are master controllers of inflammation. Mitochondrial dysfunction resulting in inflammation and immune activation is implicated in a variety of chronic non-communicable diseases, including AMD and glaucoma [14–16].

Mitochondria in Inflammation and Immunity

The processes of mitophagy, autophagy, and apoptosis are physiologically normal, and essential, for example, in embryogenesis and cell renewal [17, 18]. However, when these mechanisms are overwhelmed or disrupted, a signalling cascade ensues which results in inflammation and immune activation.

In general terms inflammation is initiated by pattern recognition receptors (PRR's) which reside on both immune and non-immune cells.

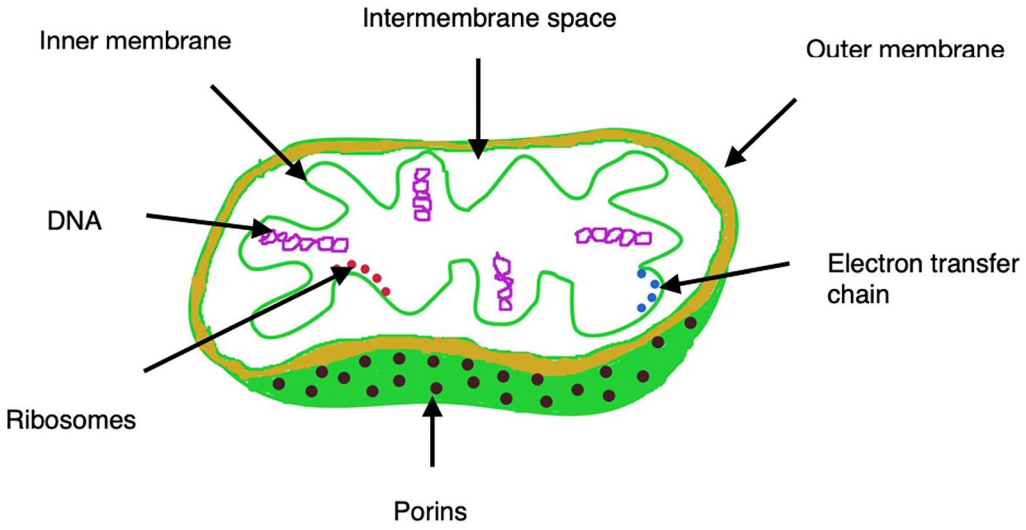


Fig. 1 Mitochondrion. Structurally mitochondria have an outer membrane consisting of a phospholipid bilayer similar to cell membranes, and an inner membrane rich in cardiolipin and omega 6 linoleic acid (LA). Between these membranes is the 'inter membrane space', and within the inner mitochondrial membrane is the 'matrix'. The outer membrane contains many integral proteins, called porins, and many enzymes. These components regulate the transport of proteins, nucleotides, ions and nutrients between the cell cytosol and the mitochondria. Diagram created using Krita software (https://krita.org/en/)

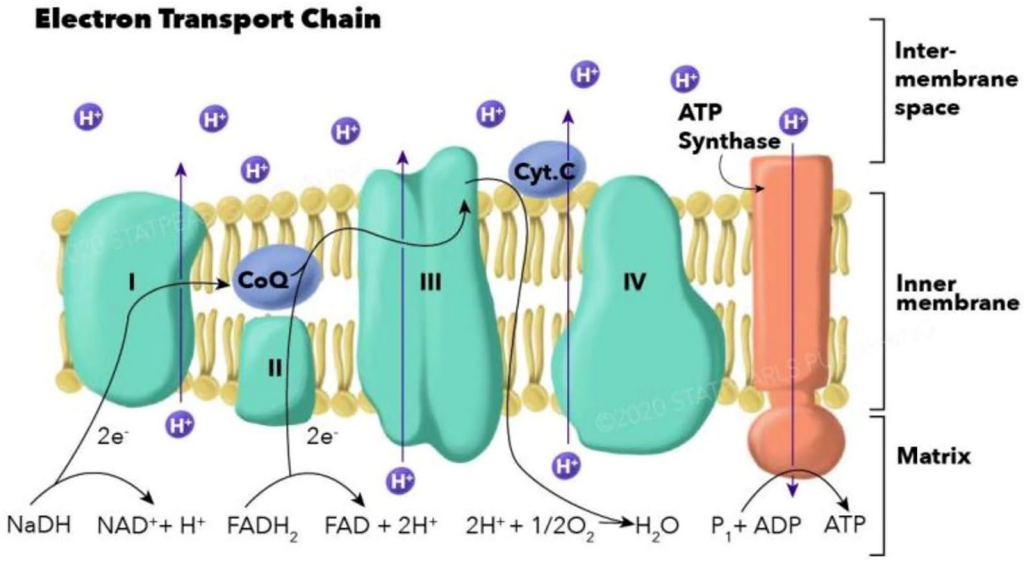


Fig. 2 Mitochondrial electron transfer chain. As electrons pass down the electron transfer chain, protons are pumped into the inter-membrane space, creating potential energy in the form of an electrochemical gradient. These protons then pass to complex V (ATP synthase), which transports the protons back into the matrix, producing ATP, the energy source for cellular processes. *NaDH* nicotine adenine dinucleotide, *FADH* flavine adenine dinucleotide, *CoQ* coenzyme Q (ubiquinone), *Cyt, C* cytochrome *c*, *ATP* adenosine triphosphate. Reproduced from National Institutes of Health (NIH) (.gov). https://www.ncbi.nlm.gov>books>NBK526105; Maria Ahmad; Adam Wolberg; Chadi I. Kahwaji; Illustration by Emma Gregory. Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) (http://creativecommons.org/licenses/by-nc-nd/4.0/)

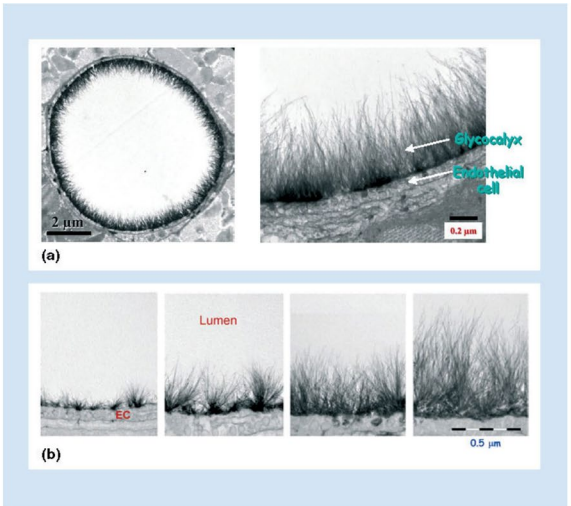
They can be activated by pathogens, such as viruses and bacteria (pathogen associated molecular patterns, PAMP's), but importantly in this context also by endogenous molecules generated as a result of cellular stress (damage associated molecular patterns, DAMP's). Impairment of the mitochondrial electron transfer chain, in response to aberrant nutrition or toxins, results in excessive reactive oxygen species (ROS) production, which may lead to increased mitochondrial membrane permeability. This can occasion cell death, with molecules such as mitochondrial DNA, mitochondrial ROS, ATP, cardiolipin, cytosol RNA and nuclear DNA entering the extra cellular space, acting as DAMP's. This results in activation of antigen presenting cells, neutrophils, dendritic cells and lymphocytes, with release of inflammatory cytokines, which may mediate vascular endothelial and systemic inflammation. Additional consequences are complement activation and priming of the adaptive immune system which are implicated in experimental autoimmune and clinical uveitis [14, 16, 19]. The activation of PRR's by PAMP's and DAMP's is a mechanism by which dysbiosis and leaky gut can contribute to systemic inflammation, autoimmunity and ocular inflammation, and this will be explored in more detail below.

The Vascular Endothelium

The vascular endothelium is critical in maintaining endothelial cell physiological homeostasis, and a barrier between the circulation and the tissues it supplies. It consists of a single layer of endothelial cells lined on the luminal side by the glycocalyx, a gel-like structure which resembles a field of grass (Figs. 3, 4).

In fact, all cells have a glycocalyx which forms part of the phenotype of the cell. The glycocalyx is fundamental to self/non-self recognition of cells by the immune system. The glycocalyx of a normal cell presents self associated molecular patterns (SAMP's), whereas a damaged cellular glycocalyx may act as a DAMP which can activate immune cells and the complement cascade. The cellular glycocalyx is also involved in signalling the age of a cell, and in the control of the migration of lymphocytes. Oxidative stress and inflammation can result in loss of sialic acid moieties of the cellular surface (Figs. 4, 5) glycocalyx immune receptors leading to complement-mediated retinal damage [20–22].

Most vessels have a continuous endothelial cell layer (including the retinal vessels),



Unhealthy glycocalyx

Healthy glycocalyx

Fig. 3 Healthy and unhealthy glycocalyx. *EC* endothelial cell. Reproduced from Vasculoprotective properties of the endothelial glycocalyx: effects of fluid shear stress; M. Gouveneur B. VanDenBerg, M. Nieuwdorp, E. Stores, H. Vink; Journal of Internal Medicine/Volume 259, Issue 4/p. 393-400; Rightslink® by Copyright Clearance Center licence no: 5876391002309

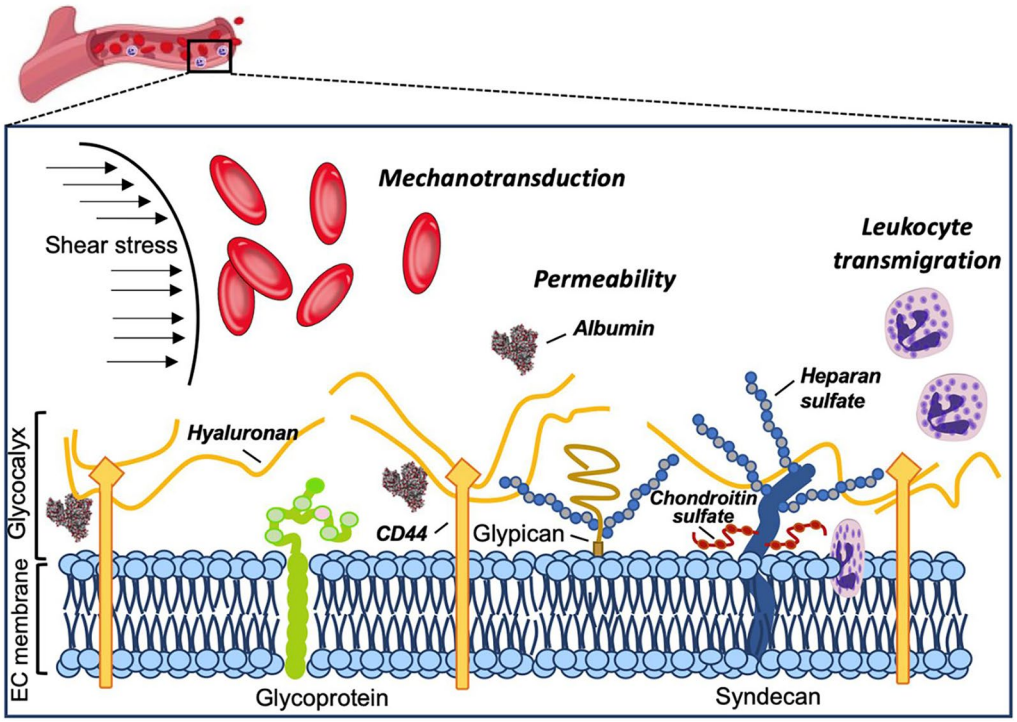


Fig. 4 Healthy glycocalyx. The glycocalyx is composed of proteoglycans, glycoproteins, and glycolipids, anchored to the endothelial cell membrane by core proteins. The glycocalyx surface is negatively charged and maintains laminar flow in vessels by repelling negatively charged plasma proteins, red blood cells and leucocytes. Other important functions include anti-inflammation, anti-thrombosis, filtration and permeability control, membrane shape regulation, regulation of growth factors and cytokine signalling and shear stress sensing which controls nitric oxide (NO) production and vascular tone [23]. CD44: receptor for hyaluronic acid; EC: Extracellular. Reproduced from N, Baby S and Yuan SY (2021) The Endothelial Glycocalyx as a Double-Edged Sword in Microvascular Homeostasis and Pathogenesis. Front. Cell Dev. Biol. 9:711003. https://doi.org/10.3389/fcell.2021.711003; Creative Commons Public Domain Mark 1.0. Creative Commons Attribution License (CC BY)

whereas the choriocapillaris and renal glomeruli have fenestrated capillaries. These fenestrations are covered by glycocalyx. Glycocalyx thickness and constituents vary with anatomical location.

Endothelial dysfunction is a feature of many diseases, including ocular diseases, and is a downstream consequence of oxidative stress and inflammation, and where aberrant nutrition, hyperglycaemia, and obesity are key contributors [24]. Systemic inflammation, oxidative stress and inflammatory cytokines all contribute to glycocalyx breakdown ('shedding') (Fig. 5) [25, 26]

THE MICROBIOME, TERMINOLOGY, AND RELEVANCE TO NON-COMMUNICABLE DISEASE

Microbiota

The micro-organisms in a specific environment, for example gut, skin, ocular surface, oral cavity and vagina. The gut microbiota consists of approximately 10^{14} organisms, about 10 times the number of cells in a human. It consists of bacteria, viruses, fungi, protozoans,

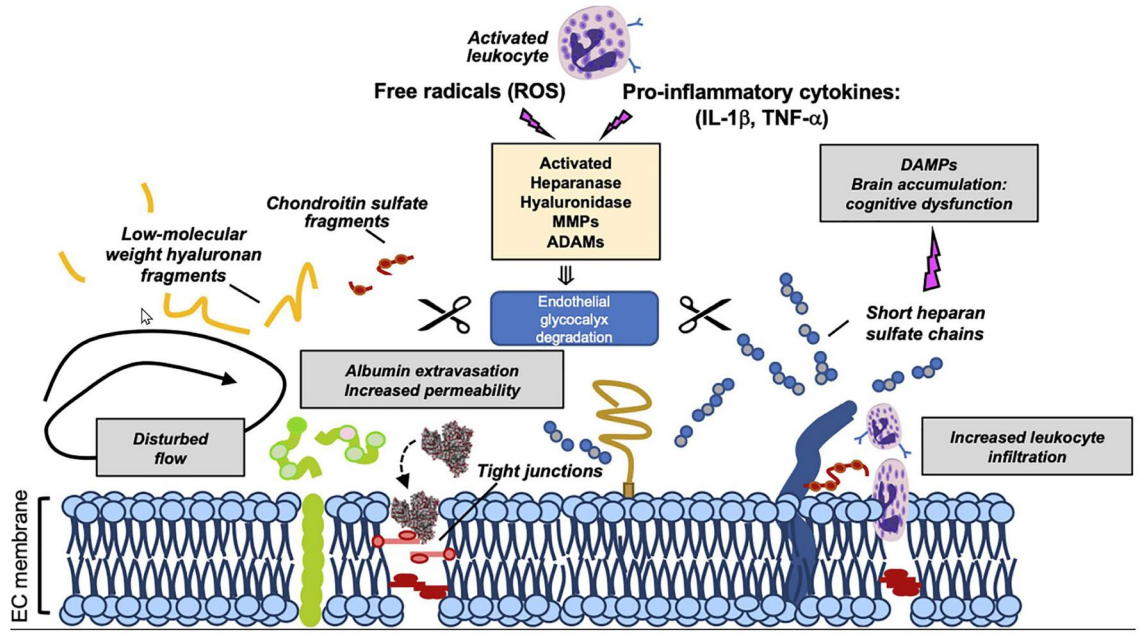


Fig. 5 Glycocalyx 'shedding'. Glycocalyx 'shedding' results in loss of barrier function, increased permeability, exposure of endothelial surface adhesion molecules (prothrombotic), leucocyte infiltration, and release of glycocalyx constituents into the circulation (DAMP's). Loss of laminar flow and 'rolling' of platelets, RBC's, and WBC's can lead to thrombosis and vascular occlusion [27] Reproduced from Nuria Villalba, Baby S and Yuan SY (2021) The Endothelial Glycocalyx as a Double-Edged Sword in Microvascular Homeostasis and Pathogenesis. Front. Cell Dev. Biol. 9:711003. https://doi.org/10.3389/fcell.2021.711003; Creative Commons Public Domain Mark 1.0. Creative Commons Attribution License (CC BY).

archaea, and is about the size of the liver. The gut microbiota develops and changes over the first few years of life, and is influenced by maternal microbiota, and the environment, as well as diet [28].

Gut Microbiome

The collective genomes of the microbiota (> 100 times human); or it may be considered to be the sum of the genes and genomes and their products and metabolites [29].

Lumen

The microorganisms, their metabolites and gut secretions.

Mucous

The mucous layer is secreted by the epithelium in response to the enteric nervous system [30]. It acts as a physical barrier, and contains antimicrobial peptides and IgA [31].

Epithelial Barrier/Tight Junctions

The integrity of the gut epithelial barrier is dependent primarily on the intercellular tight junctions. Tight junctions are composed of structural proteins: claudins, occludins and zonula occludens connected to an intracellular actin/ myosin cytoskeleton which is contractile, and thus energy dependent. Cytokines and microbial metabolites such as butyrate and indole regulate tight junction integrity [31, 32].

Immune System Development and Modulation

The gut microbiome plays an important role in the development, education, and maturation of the immune system in the neonatal period. This creates a homeostasis between inflammatory and regulatory signals involving T cell subsets (Th17/Treg), cytokines, and short chain fatty acids (butyrate, propionate, acetate). Disruption of this homeostasis is associated with childhood diseases such as asthma, food allergies, and colitis, and adult diseases such as obesity, type 2 diabetes, inflammatory bowel disease and autoimmune diseases [32, 33].

Gut-Brain Axis

This is a two way communication which is both humoral and neural. The microbiome secretes neurotransmitters and hormones, and along with vagus activity influences hunger and satiety, mood, sleep, circadian rhythm, and behaviour, with indirect effects on obesity and insulin resistance, which are important causes of chronic inflammation and vascular endothelial damage. Similarly, communication from the brain to the gut can cause dysbiosis [34]. It is now understood that a gut-retina axis exists, unsurprising since the retinal neural tissue is an extension of the brain [35].

Dysbiosis and Leaky Gut

Dysbiosis is a combination of processes resulting in:

- disruption of the 'harmonious' population of microbes in terms of number and diversity. This may result in dysregulation of metabolites which can then be toxic or beneficial to symbiotic microbes and the epithelium, and which may evoke inflammation and immunity.
- Loss of mucous layer can be caused by food additives such as emulsifiers and by a lack of fibre and prebiotics in the diet, as well as overgrowth of 'mucous eating' microbes e.g. *Akermansia*
- Loss of junction integrity: seed oils (see below), production of zonulin in response to gliadin (a wheat protein), and cytokines are all implicated

Important causes of dysbiosis are ultraprocessed foods, drugs such as antibiotics, proton pump inhibitors, and non-steroidal anti-inflammatories, nicotine, and sedentary lifestyle [36, 37]. In the setting of gut barrier breakdown and increased gut permeability, food components e.g. lectins, microbes, microbial products and components (lipopolysaccharides, LPS), beta glucan (PAMP's and DAMP's) come into contact with the gut associated lymphoid tissue (GALT), potentially activating both innate and adaptive immune systems [33]. Oral pathobionts present in oral dysbiosis are also implicated in leaky gut syndrome [32].

Mechanisms by Which Gut Permeability May Contribute to Auto Immunity and Uveitis

It is postulated that there are four mechanisms by which dysbiosis may cause autoimmune uveitis:

- Antigenic mimicry
- Loss of intestinal immune homeostasis
- Loss of intestinal barrier with increased gut permeability
- Alteration of microbial metabolites [38]

Antigenic (molecular) mimicry: cross reactivity of microbiota derived peptides with self antigens generates autoreactive T cells [39, 40]. This is supported by the rodent model of experimental autoimmune uveitis (EAU) [41] and CNS autoimmune diseases, such as Multiple Sclerosis [42] and Neuromyelitis Optica [43]. Probiotics have been shown to have a beneficial effect on both EAU [44] and experimental autoimmune encephalitis [45].

Loss of intestinal immune homeostasis: loss of balance between inflammatory Th17 T cells, and modulatory Treg T cells. This is

implicated in dysbiosis associated with Behcet's and autoimmune uveitis, [46] and Vogt–Koyanagi–Harada disease [47]. Activation of innate immune responses, inflammatory T-cell balance and circulating inflammatory cytokines may all have remote inflammatory effects.

Alteration of microbial metabolites: Short chain fats acids (SCFA), predominantly synthesised by micriobiotal fermentation of dietary fibre, are an important energy source for intestinal epithelial cells and account for about 10% of energy harvest in humans. They have an anti-inflammatory effect by increasing Treg cells, and reducing transfer of activated T cells from the gut to the spleen [38]. Recently, research has demonstrated the presence of an intraocular microbiome, with possible correlations with ocular diseases such as age related macular degeneration, glaucoma [48], and diabetic eye disease [49]. The mechanisms by which these bacteria pass through the blood ocular barrier have not been elucidated, but it would be logical to hypothesise that vascular endothelial dysfunction as described above, could be contributory. What role, if any, these intraocular organisms may play in ocular autoimmune diseases is unclear at this stage.

Interest in the association and importance of the microbiome in systemic diseases has grown dramatically over the past decade or so, with relevance to many diseases such as multiple sclerosis, autism, Alzheimer's, epilepsy, Parkinson's, stroke, obesity, metabolic syndrome, cancer, autoimmunity and ocular disease [33]. Experimental studies in rodents have shown positive outcomes on EAU and EAE, especially in germ free rodent models [44, 45], and in obesity in humans, by manipulating the microbiome with probiotics and prebiotics [50, 51]. However, the effects of probiotics on disease are complex, and unpredictable, since effects are often strain specific not simply phylum or species specific [52]. Furthermore probiotic supplements do not generally recolonise within the microbiota, and may even impair natural recolonisation of a disturbed microbiota [53]. Prebiotics, mainly in the form of fibre, have been shown to have a beneficial effect on microbiota balance and microbiota metabolite (e.g. SCFA) production [51].

Faecal Microbial Transplantation (FMT)

FMT is a procedure involving direct transfer of microbiota from a healthy animal or patient to an unhealthy one. FMT in the rodent model is a useful tool in researching the effects of the microbiome on metabolic function, inflammatory diseases and behaviour [54–56]. In humans, FMT has been shown to have a beneficial effect in Clostridium Difficile colitis [57], and to a lesser extent in ulcerative colitis [58]. In principle, FMT represents a promising avenue of research and therapeutics for a variety of diseases in humans, although methodology, including control of inputs, such as diet, need to be standardised [59], and safety needs to be assured.

To summarise, the gut microbiome is complex and dynamic. It is required for 'training' the immune system in infancy and maintaining the homeostatic balance between inflammatory and regulatory signals that is required for optimal health. Changes in inflammatory or metabolic state associated with changes in the microbiome are therefore most likely related to a change in the balance of signals, rather than to a change in a single micro-organism or metabolite. The existing microbiome, and inputs such as nutrition, lifestyle, and drugs all influence the effects that the microbiome can exert on health and disease.

ABERRANT NUTRITION AND MITOCHONDRIAL DYSFUNCTION: WHAT IS THE ROLE OF SEED OILS AND SUGAR?

Previous sections have introduced the concept that the aetiology of many chronic non-communicable diseases is founded in mitochondrial dysfunction, inflammation, vascular endothelial dysfunction, and dysbiosis. A summary of the role that diet and lifestyle play in contributing to these processes follows.

Obesogens

Obesity itself is an inflammatory state, and causation is multifactorial incorporating energy balance, hyperinsulinaemia, oxidative stress

and environmental toxins, with the balance of effects at the cellular level, reducing mitochondrial efficiency [13]. Environmental toxins may be found in plastic food packaging, unfiltered water, pesticide residues on fresh foods, and particles in the air we breathe. The modern 'Western' diet, comprised of approximately 65% ultra processed foods contains an unhealthy balance of energy substrate, lack of nutrients and obesogens in the packaging.

Seed Oils

The dramatic rise in dietary 'oils and fats' is comprised of mainly industrially produced seed oils ('vegetable oils') rather than saturated fats from animal and dairy sources. Seed oils are polyunsaturated fats (PUFA) containing a high proportion of linoleic acid (LA), as well as varying amounts omega 3 alpha linolenic acid (ALA) [60]. Both classes of PUFA are 'essential' in small amounts for important functions such as membrane integrity, immune function, neural development, regulation of inflammation, coagulation and cell signalling. In 1865, prior to the introduction of seed oils, dietary consumption of LA was approximately 2 g/day. By 2018 this had reached approximately 80 g/day. This dramatic increase has been promoted by use of seed oils for cooking, inclusion of seed oils in many ultra processed foods, and health policies which have encouraged PUFA consumption [60]. Unfortunately, excessive LA consumption results in a systemic pro inflammatory milieu owing to the competitive nature of the delta 5 and delta 6 desaturase pathways in the metabolism of LA and ALA [60]. It also contributes to visceral adiposity, which in itself is pro-inflammatory. Much of the excess dietary LA is peroxidised (as a result of shelf storage, and by high temperature cooking). Incorporation of peroxidised LA into the inner mitochondrial membrane causes cardiolipin remodelling [60–62]. This results in conformational changes in the inner mitochondrial membrane, which reduces the efficiency of electron transfer and ATP production, promotes de-novo lipogenesis and increases ROS production in excess of antioxidant mechanisms. In the context of Western diet, the excessive ROS production is compounded by excessive dietary substrate (in the form of fatty acids (FA) and glucose) supplied to the mitochondrial matrix for oxidative phosphorylation [63]. This high level of ROS, and the effect it has on calcium signaling, can result in opening of the mitochondrial permeability transition pore in the inner mitochondrial membrane, resulting in proton leakage and diffusion of matrix chemicals into the intermembrane space. This can lead to mitochondrial disruption, apoptosis and in extreme cases, cell necrosis [14].

Sugar

Excessive added sugar in the diet has been correlated with the increase in non-communicable diseases. Sugar consumption in the USA increased from 2.9 kg/year in 1822 to 49 kg/year in 1999, a 17 fold increase. This does indeed correlate well with non-communicable diseases, and especially obesity and diabetes until about 1999, when sugar and refined carbohydrate consumption started to decline, while seed oil consumption continued to rise, and obesity and diabetes continued to increase [60]. Dietary sugar (sucrose and high fructose corn syrup) is approximately 50% glucose and 50% fructose. Glucose is needed for cellular energy production, especially by the brain, but the body's dietary requirement for glucose is low, as the liver can produce adequate glucose for metabolic functions via gluconeogenesis. Excessive dietary glucose can contribute to insulin resistance, dyslipidaemia and de-novo lipogenesis (DNL). The fructose in added sugar is far more metabolically harmful. When metabolised, it downregulates mitochondrial energy production, produces 100 × the oxygen radicals (oxidative stress) that glucose does, and drives protein glycation 5 × faster than glucose [64]. Furthermore, uric acid, and methylglyoxal, end products of fructose metabolism, promote production of pro inflammatory cytokines, stimulate renal inflammation causing hypertension, enhance insulin resistance and DNL, reduce vascular endothelial nitric oxide (NO) production and inhibit

autophagy by reducing intracellular AMPk production [64].

Any factor which adversely affects vascular endothelial glycocalyx and vascular endothelial function (e.g. inflammation, hypertension, hyperglycaemia, hyperinsulinaemia, impaired NO production) can act as a prerequisite for vascular inflammation, vascular occlusion, increased vascular permeability, and blood-ocular barrier breakdown, all of which are relevant to ocular conditions such as diabetic retinopathy, retinal vasculitis, retinal vascular occlusion, macular oedema and uveitis.

In summary it is now apparent that the Western dietary excess of seed oils, sugar and obesogens commonly contained in ultra processed foods contribute to non-communicable diseases by downregulating cellular energy production, increasing oxidative stress, and promoting inflammation and vascular endothelial dysfunction.

THE LIFESTYLE CONNECTION

There is evidence of the interconnected effects of lifestyle, namely, exercise, sleep, stress management and sunlight exposure on metabolic health, and therefore by extension chronic non-communicable systemic and ophthalmic disease.

Exercise

Exercise in itself is medicine, a concept that is not new [65]. There is ample evidence in the literature that exercise has beneficial effects for all cause mortality [66–68], metabolic health, insulin resistance, glucose and lipid metabolism [69–72], mental health [73], sleep [74] and the gut microbiome [75, 76]. Not surprisingly, many of the benefits of exercise on health are mediated by improvements in mitochondrial function and signalling [77–81].

Sleep [82]

Normal, healthy sleep duration is 7–9 h. Short sleep duration and long sleep duration are both associated with increased all cause mortality [83, 84]. In the case of short sleep this can be causally associated with effects on metabolism [85]. In the case of long sleep it may be associated with underlying comorbidities, particularly those related to mental health. Better sleep is associated with better mental health [86] and this in turn leads to healthier diet and behaviour. Short sleep is potentially causally linked to Alzheimer's disease [87], and sleep disturbance is a feature of Alzheimer's [88]. Metabolic dysfunction and impaired bioenergetics are increasingly recognised in the aetiology of Alzheimer's [89, 90], and it is plausible that the same mechanisms could play a role in ophthalmic diseases. Other associations between sleep and eye diseases such as 'floppy eyelid syndrome' and anterior ischaemic optic neuropathy have been noted [91]. Sleep also affects immune function [92], and from first principles it would be reasonable to infer that systemic and ocular immunity may be affected.

Stress

While there is no obvious direct link between 'stress' and ocular disease, stress is very much correlated with hypothalamic–pituitary–adrenal axis (HPA) dysregulation [93, 94], and HPA axis dysregulation has marked effects on metabolic function and its associated diseases [95]. Increased cortisol secretion as part of the stress response results in increased intracellular ceramide production, which leads to mitochondrial dysfunction, insulin resistance and inflammation [96]. Via these mechanisms there is an indirect effect on ophthalmic disease.

Sunlight

From an evolutionary perspective, humans evolved to live in harmony with the day-night cycle. This has resulted in the 'circadian rhythm' of metabolic and endocrine changes that occur in response to light exposure and darkness [97]. The most commonly known is the synthesis of cholecalciferol (vitamin D3) in the skin in response to the UV-B in sunlight (300 nm wavelength). Vitamin D increases intestinal absorption of calcium, phosphate and magnesium

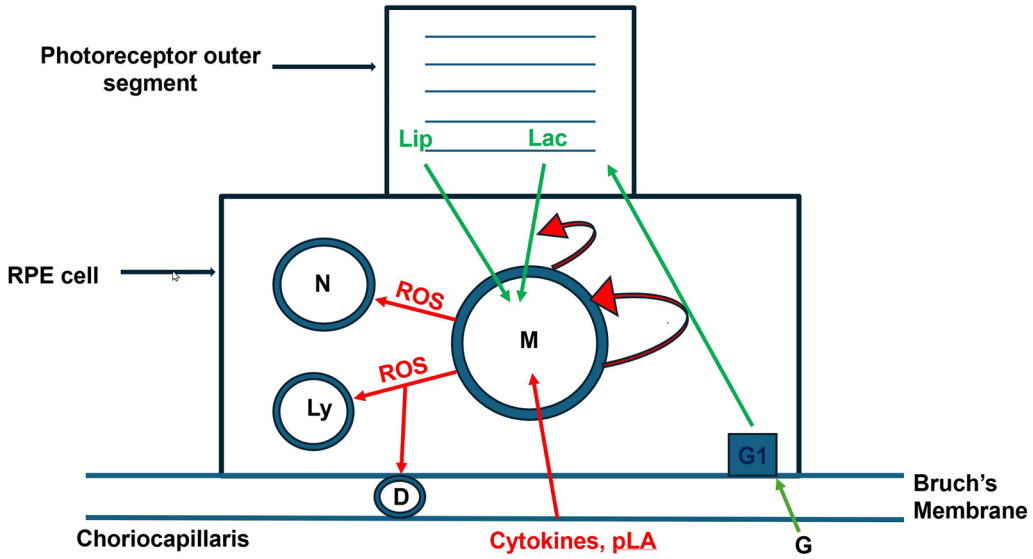


Fig. 6 Schematic of RPE dysfunction in AMD. *M* mitochondrion, *N* nucleus, *Ly* lysosome, *D* druse, *G* glucose, *G1* Glut 1 glucose transporter, *ROS* reactive oxygen species, *Lac* lactate, *Lip* lipid, *pLA* peroxidated linoleic acid. In a healthy situation (green) glucose is transported from the choriocapillaris across the RPE cell to the photoreceptor outer segment for energy production by glycolysis. The lactate produced is passed back to the mitochondria to enter the Krebs cycle. The mitochondria also obtain energy substrate from photoreceptor outer segments being recycled. In obesity and aberrant nutrition (red) inflammatory cytokines (TNFα, IL6, TGFβ2, IL-1β) and peroxidated linoleic acid impair mitochondrial function, increasing ROS production. This results in inhibition of lactate return to the mitochondria, and diversion of glucose intake to the mitochondria, reducing energy substrate to the photoreceptor outer segments. The increased ROS also affect synthesis of electron transfer chain production mediated by mitochondrial DNA, and disrupt nuclear function. In addition, the autophagy/phagocytosis pathway is disrupted, resulting in accumulation of intracellular debris, drusen formation, choriocapillaris atrophy, further inflammation and neovascularisation.

and is essential for bone health. However, vitamin D is also involved in immunomodulation, regulation of cell proliferation, blood pressure regulation, and insulin production [98]. UV-B also stimulates pineal melatonin production, important in sleep and circadian regulation. Less well known is the important effect of the red/near infra-red (R/IR) (670–850 nm) wavelengths in sunlight. These wavelengths penetrate deep into tissues, including into the brain, uprate mitochondrial energy production and stimulate cellular mitochondrial melatonin production. Melatonin is a potent antioxidant, and is integral to metabolic health [99–101]. It is notable that modern office lighting lacks R/IR spectrum, and this may be contributory in the epidemic of chronic non-communicable diseases.

RELATIONSHIPS TO COMMON EYE DISEASES

Age Related Macular Degeneration (AMD)

The increasing prevalence AMD correlates well with the increase in chronic non-communicable diseases generally. In the early 1900's AMD was almost unknown. In the 1930 there were approximately 50 cases in the world literature. In 1940, Duke-Elder described it as 'common' in his textbook, and by 2014 it had become the commonest cause of blindness in people over the age of 65 [60, 102]. Recognised associations, often misnamed as 'risk factors', include age, smoking, cardiovascular disease, sedentary lifestyle, obesity, diet high in ultra processed foods and hypertension [1]. It is important to note

that age and cumulative exposure to environmental factors usually co-exist as risk factors in the aetiology of these diseases, including AMD. A recent study of a biomarker known as Metabolic Vulnerability Index (MVX) found that age was not an independent predictor of all cause mortality [103]. It may be that 'exposure', combined with genetic factors is more important than age in the development of age related macular degeneration.

AMD involves pathological changes in the choriocapillaris-RPE-photoreceptor complex, which is a highly metabolically active area. The RPE exhibits trophic effects on both the choriocapillaris and the photoreceptors, and the photoreceptors in turn exhibit trophic effects on the RPE [104]. Energy production in the photoreceptor outer segments is predominantly by aerobic glycolysis, with the RPE transporting glucose from the choriocapillaris to the photoreceptors via non-insulin dependent GLUT-1 transporters. The photoreceptor inner segments have abundant mitochondria. The RPE cells themselves metabolise hardly any glucose, and obtain their energy from oxidation of lactate (resulting from photoreceptor outer segment glycolysis), fatty acids and ketone bodies endogenously synthesised in the mitochondria, the substrate for which comes from the phagocytosis and breakdown of photoreceptor outer segments (about 10% per day) which occurs as part of the visual cycle [104]. While genetic associations with AMD susceptibility are well known, mitochondrial dysfunction in the RPE plays an important role in the cellular and pathological features of AMD.

Impairment of RPE mitochondrial energy production by environmental and dietary disruptors results in oxidative stress from ROS production which exceeds the anti oxidative mechanisms in the mitochondria. ROS oxidise proteins, lipids, nucleic acids and lipoproteins. Damage to the mitochondrial DNA, particularly the areas which encode the electron transfer chain proteins, compounds the impaired energy production. Proteostasis, which is the coordinated regulation of protein synthesis, folding and degradation is disrupted, as are the lysosomal and autophagy pathways. Accumulation of lipofuscin and cytoplasmic aggregates ensues, leading to inflammation, which exacerbates RPE dysfunction [105] and chronic activation of innate and adaptive immunity [106]. Drusen, which are deposited between the basement membrane of the RPE and inner collagenous layer of Bruch's membrane potentiate inflammation, and can impair transport of nutrients and oxygen across the RPE cells, with the consequent downstream effects of photoreceptor degeneration, RPE and choriocapillaris atrophy and neovascularisation [107, 108] (Fig. 6).

Primary Open Angle Glaucoma (POAG)

The prevalence of POAG in 2006 has been estimated at 4.2% in Black populations, 2.1% in white populations and 1.4% in Asian populations. In white populations the prevalence rises from 1.8% in the 30–39 years age group, to 16.9% in the 80–89 years age group [109]. Primary open angle glaucoma is an optic neuropathy characterised by retinal ganglion cell (RGC) apoptosis. Intrinsic apoptosis is controlled primarily by the mitochondria [110]. In the light of our knowledge of the role of mitochondrial in bioenergetics and inflammation, it is logical to hypothesise that impaired bioenergetics, insulin resistance, and neuroinflammation play an important part in RGC dysfunction and death [16, 111, 112] (Fig. 7).

In many, but not all cases, RGC loss in glaucoma is associated with elevated intraocular pressure, and elevated intraocular pressure in itself increases oxidative stress in the optic nerve head. 'Low tension glaucoma' is a well recognised phenomenon, and has many of the associations that exist with other chronic non-communicable diseases, namely age, systemic hypertension, nocturnal hypotension, migraine, Raynaud phenomenon, dementia, obstructive sleep apnoea, smoking and steroid use. Correlation between features of metabolic syndrome and POAG has been reported [113]. Family history is an important 'risk factor' for POAG and normal tension glaucoma (NTG), although genetic mutations play only a small role in the aetiology. This raises the possibility that epigenetic changes recognised to be induced

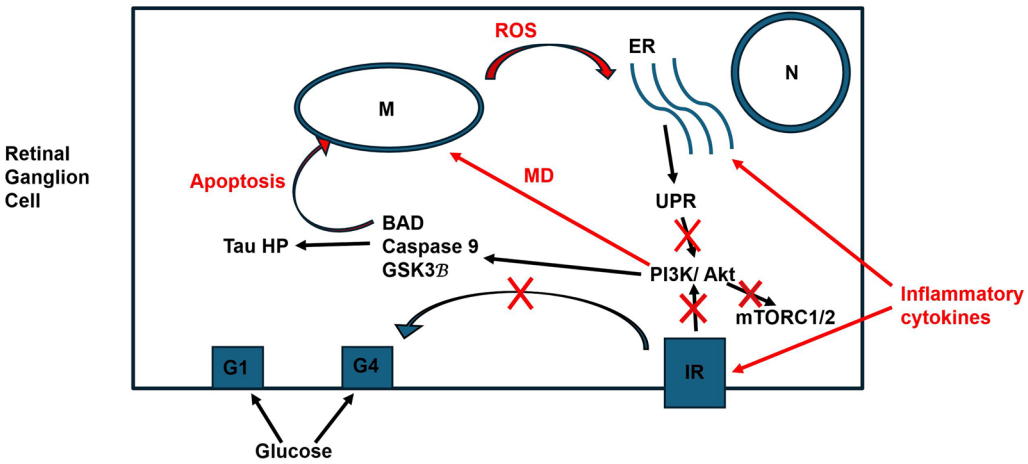


Fig. 7 Schematic of retinal ganglion cell showing effects of systemic inflammation and insulin resistance. *IR* insulin receptor, *M* mitochondria, *N* nucleus, *G1* Glut1 glucose transporter, *G4* Glut 4 (insulin dependent) glucose transporter, *ER* endoplasmic reticulum, *ROS* reactive oxygen species, *MD* mitochondrial dysfunction, *UPR* unfolded protein response, *mTORC1/2* mammalian target of rapamycin complex, *PI3K/Akt* phosphoinositide-3 kinase, protein kinase B, *BAD* bcl-2 agonist of cell death, *GSK3β* glycogen synthase kinase 3-β, *TauHP* Tau protein hyperphosphorylation. Systemic inflammatory cytokines and endoplasmic reticulum stress cause insulin resistance in the RGC. While the insulin resistance may reduce glucose entry to the RGC via the Glut4 transporter, reducing energy substrate, glucose is also transported via Glut1. More importantly the anabolic and cell maintenance effects of insulin are impaired, resulting in mitochondrial dysfunction, excessive ROS production and apoptotic signalling

by environmental factors including diet, lifestyle and environmental toxins, and which are known to be intergenerationally transferable, may be involved.

In the context of a bioenergetic and neuroinflammatory hypothesis of RGC apoptosis in glaucoma, research in psychiatric and neurodegenerative conditions is instructive. Ketogenic diet has been used effectively in the treatment of epilepsy for over a hundred years [114]. Preclinical studies have also demonstrated the efficacy of the ketogenic diet in Alzheimer's disease [115]. It has been widely thought that neural tissues are obligate in their use of glucose as metabolic fuel. In fact neural tissues are capable of using ketones for up to 60% of their energy needs. Ketones produce less oxidative stress when metabolised, and are anti-inflammatory [116]. It is now understood that in Alzheimer's dementia, intraneuronal energy starvation and neuroinflammation, both caused by systemic metabolic dysfunction including insulin resistance are implicated [15, 89, 117]. Dietary interventions have proven effective in treating neurodegenerative and psychiatric conditions [115], and Nutritional Psychiatry is a rapidly evolving sub-specialty [118, 119]. While a bioenergetic and neuroinflammatory hypothesis for RGC apoptosis in glaucoma is scientifically plausible and logical, studies of dietary interventions which address systemic metabolic health for the treatment of POAG are lacking.

If it is possible that impaired bioenergetics plays a part in RGC apoptosis in glaucoma, could it also be involved in dysregulation of aqueous outflow at the trabecular meshwork? The trabecular meshwork in the iridocorneal angle is formed by connective tissue beams and lamellae covered by trabeculocytes. There are three regions of the trabecular meshwork: uveal, corneo-scleral and juxtacanalicular. The latter abuts the endothelium of Schlemm's canal, and controls the permeability of the endothelial cells. Resistance to outflow is at the level of the juxtacanalicular meshwork [120] and is dependent on the regulation and

turnover of extracellular matrix proteins at this level. This is an energy dependent, and thus mitochondrially dependent process. Mitochondrial dysfunction in the trabecular meshwork might therefore be expected to result in increased outflow resistance and elevated IOP, and mitochondrial dysfunction in trabeculocytes has indeed been demonstrated in POAG [121, 122]. There is also evidence that trabecular extracellular matrix (ECM) alterations in response to pro-inflammatory DAMP's may be implicated in increased outflow resistance [16].

In summary, it is plausible, and likely, based on published science that RGC apoptosis in POAG and LTG is a result of impaired cellular energetics and neuroinflammation secondary to mitochondrial dysfunction. Similarly, it is likely that dysregulation of IOP control in the trabecular meshwork is also secondary to mitochondrial dysfunction.

Diabetic Retinopathy

Diabetic retinopathy is characterised by increased retinal capillary permeability, pericyte loss, microaneurysm formation, retinal ischaemia, and retinal neovascularisation. Retinopathy is recognised in the setting of overt hyperglycaemia. In reality, hyperglycaemia in type 2 diabetes is a late stage in usually decades of underlying metabolic syndrome and hyperinsulinaemia. The result is chronic inflammation and vascular endothelial damage. The underlying mechanisms can be easily inferred from the sections above: glycocalyx shedding, increased endothelial cell adhesion molecule expression, loss of endothelial barrier function and inflammation and oxidative stress.

This is comprehensively reviewed by Forrester et al. [123]. Retinal function as measured by electroretinography is measurably decreased prior to the development of retinopathy [124].

Ischaemia, mitochondrial dysfunction or impaired endogenous insulin signalling in the RPE and photoreceptors, which precede retinopathy may all be implicated [125, 126]. On the same principles that a gut-brain axis has been established, a gut-retina axis has been proposed, and is eminently plausible [35]. Whereas considerable resources have been devoted to the treatment of diabetic complications, insufficient attention has been paid to prevention by addressing the underlying cause and process, namely insulin resistance and metabolic dysfunction resulting from inappropriate diet and lifestyle.

ROLE OF THE OPHTHALMOLOGIST

The primary role of the ophthalmologist is to treat ocular disease and mitigate the harmful effects of ocular disease on ocular and systemic health. However, there is an argument that in Ophthalmology, as in many subspecialties, the modern medical paradigm has moved too far towards managing disease, to the exclusion of managing the causes of disease.

In this context there is a place for greater awareness of the scientific principles of disease in clinical practice, and for them to be given more prominence in undergraduate and postgraduate medical curricula. This is important if it is accepted that chronic ophthalmic diseases are part of the spectrum of chronic non-communicable diseases, with a shared common aetiology. There are significant implications for future morbidity from metabolic syndrome, type 2 diabetes and early all cause mortality [127–129].

Many patient presentations to Ophthalmology clinics relate to as yet undiagnosed underlying systemic diseases, especially metabolic dysfunction, many of which are nutrition and lifestyle related. While it is not the role of the Ophthalmologist to provide detailed nutrition and lifestyle advice, as clinicians, we all have a 'duty of care', and there is a role for Ophthalmologists in recognising underlying systemic disease. Simple routine clinical and laboratory investigations can be performed facilitating a more informed liaison with other health practitioners involved in managing the systemic health of the patient. Adding nutritional and lifestyle interventions to existing treatment regimes may improve health and disease outcomes, and in many cases can reduce

or eliminate pharmaceutical dependence. This would of course require adequate resources for dietary and lifestyle counselling and behavioural support [130].

RESEARCH IMPLICATIONS

Chronic ocular diseases typically constitute a significant proportion of an Ophthalmologist's workload. Ophthalmologists are therefore well placed to carry out research to investigate and elucidate the associations between metabolic health (a proxy for nutrition and lifestyle) and chronic Ophthalmic (and systemic) disease. While food questionnaires are notoriously unreliable, metabolic, inflammatory, and vascular health is readily objectively assessed using a variety of laboratory and imaging investigations [24, 127–133].

Routinely used, and newer Ophthalmic imaging techniques allow quantification of Ophthalmic diseases such as age related macular degeneration and glaucoma [134–139]. Integrating these approaches with metabolic and microbiome research would represent an opportunity to inform all these fields, with enormous potential to improve health and mitigate disease.

CONCLUSIONS

Current medical practice involves a predominantly downstream treatment approach which is focussed on disease. While this does mitigate morbidity, and improves lifespan, it does not positively influence healthspan to the same degree. In some cases, for example in Alzheimer's, this approach is ineffective. There is a strong argument for 'looking backwards', in other words taking an upstream approach to disease, by addressing the cellular processes which cause disease. This applies to systemic and ophthalmic disease, and has been shown to be effective for example in nutritional psychiatry and type 2 diabetes.

By continuing to ask 'why' diseases occur, and following the underlying science it is apparent that the majority of non-communicable diseases share common cellular and pathophysiological characteristics. These are impaired cellular energetics, inflammation, and vascular endothelial dysfunction. They are inextricably interconnected and governed by environmental inputs: diet, exercise, sleep and stress, all of which are modifiable by behaviour change.

Mitochondrial function, and the gut microbiome are the key influencers of metabolic function and inflammatory state. Dietary substrate, as well as providing fuel for energy production and cellular maintenance, also influences the immunomodulatory and hormonal signalling functions of the microbiome. Mitochondria are the controllers of fuel utilisation for energy balance and proteostasis. They are also master controllers of inflammation and apoptosis. The Western diet, which contains excessive PUFA and fructose has a profound effect on mitochondrial function. It results in downregulation of energy production and autophagy, stimulation of de-novo lipogenesis, excessive ROS production, disruption of proteostasis, induction of insulin resistance, production of inflammatory mediators and apoptosis.

The inflammatory milieu induced by mitochondrial dysfunction, gut dysbiosis and adipose inflammation adversely affects vascular glycocalyx and endothelial function, which underlies the role in autoimmunity, vascular inflammation, vascular occlusion and vascular endothelial barrier function.

The intention of this review has been to provide a balance between detail, and the overall picture. The references are designed to provide resources for readers who wish to pursue any of the topics in more detail, for personal interest or for informing research projects. To finish with a favourite quote, by Don Campbell, Canadian rancher speaking on the subject of regenerative farming: it applies to our paradigm of medical practice, which needs to change. 'If you want to make small changes, do things differently. If you want to make big changes, see things differently'.

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