The Eye as a Window to Wellness

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Introduction

Chronic non-communicable diseases (NCDs) contribute 53% to the global disease burden, killing close to 38 million people globally, every year. Over 20% of the country lives with at least one NCD, the costs of which are expected to mount to $6.2 trillion by 2030, if not treated appropriately (1). Some of the most common conditions include cardiovascular diseases, stroke, diabetes and cancer.

Modern day medicine, known to make waves in innovative and easy technological approaches, has made scientists shift focus to more effective, non-invasive methods for early-screening of such chronic conditions, their latest focus being the eye, and justifiably so.

The Eye: A Window to Human Wellness

Philosophers have long described the eyes as the "window to the soul" but of late, medical science has deciphered a logical connotation to this expression (2). Anatomical, developmental, (immune) functional and (to an extent) physiological similarities between the eye, the brain and the heart have helped researchers decipher hidden tools to screen for early stages of damage to these vital organs of the body.

On one hand, we have the retinal neurovascular architecture and the retinal ganglion pathways leading us to the microvascular environment of the central nervous system, on the other hand similarities between the heart and the eye in terms of responses to intrinsic and environmental stimuli make the eye, a window to the heart as well (2) (3) (4). Not only this, deposition of various chemicals in the eye are also indicative of chronic conditions like inflammation and cancer, which further emphasizes on the fact that eyes reveal more than just vision-related anomalies (5).

A comprehensive, dilated eye-examination can be used to detect the advancement of disease, monitor the efficacy of treatment regimens and record ocular manifestation of medications used to treat chronic conditions. This enhances the possibilities for reduced treatment costs, and subsequent improved adherence and treatment outcomes (6).

Ophthalmologic Screening: Crucial Aspects

The retina, situated in the inner part of the eye contains retinal ganglion Cells (RGC) comprising the innermost cellular layer of the retina that project their axons across the inner retina in the form of the Retinal Nerve Fibre Layer (RNFL), thickest at the optic disc (OD), gradually leading to the brain and the CNS via the optic nerve. The inner layer of the retina is washed by the central retinal artery, running alongside

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the optic nerve. The fovea, responsible for sharp color mediated vision, lies in the centre of the macula (3).

It can thus be said that the retina is an extension of the CNS and can easily be viewed non-invasively via several imaging modalities.

Fundus Camera Imaging is one of the more popular modalities which analyses the retina in the form of two-dimensional colour photographs of the interior, three-dimensional surface of the eye. Fundus imaging provides a clear picture on the microvascular health of the individual with fine details on vessel diameter, vascular tortuosity and bifurcation geometry of the retina. Owing to such specificities, fundus images are a potent identifier of lesions and haemorrhages. This technique has been declared as a validated tool for Diabetic Retinopathy (DR) screening (3).

Smartphone based fundus cameras like the Remidio NM FOP from Remidio Innovative solutions, uses patented optics based on an annular illumination design that separates the illumination and imaging paths to provide reflex-free, high quality retinal images for enhanced diagnosis. The device has been validated to provide high quality retinal images similar to that found in current desktop cameras (7).

A **Scanning Laser Ophthalmoscope (SLO)** uses less than 1/1000th of the light necessary to illuminate the fundus with conventional light ophthalmoscopy (8). Similar to fundus camera imaging, SLO also uses two-dimensional imaging technique but employs a laser beam to scan through the three-dimensional surface of the retina to generate high-contrast, finely-detailed images. It has a larger field of view in a single image as compared to the fundus camera and is used to examine the fundus features in the peripheral retina. SLO devices may produce images with lower resolutions compared to fundus cameras, which, added to the cost and complexities of the devices, make its use limited to research and selected ophthalmology clinics and that too only in the developed world (3).

Another popular imaging modality is **Optical Coherence Tomography (OCT)** which is a non-invasive and non-contact method employing near-infrared light to penetrate the retina and uses interferometry to resolve tissue layers within the eye. Such a technique allows cross-sectional viewing of the internal retinal structures and to assess changes in the RNFL, a potent biomarker for neurodegeneration (3).

Fluorescein Angiography (FA) involves an intravenous injection of a fluorescent dye while illuminating the retina at a suitable excitation wavelength to get an improved and contrasted detail of the ocular vasculature. This helps to keep a check on ocular flow-velocity, leakages, blockages and related pathological conditions wherever the dye is seen to escape into the surrounding tissues, by capturing a timely sequence of relevant images (3). Remidio's ANGIO-ON-TOUCH (AOT) is one example of such a device.

Multimodal imaging techniques that combine two or more modalities (mostly SLO and OCT) are being used increasingly to obtain high-quality images with minimum motion artefacts and noise and provide seamless localization of the same retinal spots between patient visits; thus helping in measurement of longitudinal changes.

Implementing various software-based tools with multimodal imaging system augments the analytical potential of such modalities, enabling qualitative and quantitative measurements of morphometric properties and their deviations in patients with chronic conditions. Using specialised softwares, annotated data and classified algorithms help in detecting retinal lesions, assess retinal textures, retinal vessel tracking and segmentation, aberrations in vessel geometry, determining arteriole-to-ventriole ratio (AVR), complexities in branching patterns of vessels, quantification of optic nerve heads and analysing optic discs. Using computational fluid dynamic simulations to fundus images helps to assess structural changes in vasculature, detect abnormal blood-flow patterns, potential threats to retinal microcirculation and screen for subsequent chronic conditions (3).

Ocular Manifestations of Common Chronic Diseases

Since the retina is devoid of an autonomic nervous system of its own, it is controlled by local and circulating factors such as local metabolic demands, blood pressure, oxygen and carbon dioxide levels, linking it to the nearby organs like the brain and the heart, both of which are crucial in sustaining life (9).

Cerebrovascular Diseases: Hypertension & Stroke

The microvascular and ontogenic similarities between the cerebral and retinal circulation consist of endothelial cells, pericytes, basement membranes and microglial cells which are responsible for providing physical, nutritional and metabolic support by maintaining a constant exchange of vital humoral proteins, blood-brain barrier proteins, metabolic factors (like endothelins, arachidonic acid metabolites, histamine, dopamine, acetylcholine, vasopressin, sodium and potassium, calcitonin and gene-related peptides, to name a few) releasing pivotal growth factors and regulating degeneration and regeneration of retinal and cerebral tissue. Homeostasis between cerebral blood flow over a range of systemic blood pressures and their vascular resistance is maintained by the vascular smooth muscles of the cerebral and retinal arterioles and pericytes (8).

With such similarities in vasculature and circulation, **ageing** also has an equally proportional impact on both the retina and the brain. Reduced cerebral blood-flow, decreased metabolic rates and the gradual wear and tear of tissues and vasculature, basement membrane thickening, and a decrease in endothelial and pericyte cell populations are some of the adverse-effects noticed within ageing populations.

Impaired vascular circulation also leads to increased systolic blood-pressure gradually leading to **hypertension**.

Hypertension has evidently been related to increased peripheral vascular resistance, reduced AVR and arterial narrowing (leading to microaneurysms, exudates and haemorrhages) in previously conducted clinical studies, the Rotterdam study from Netherlands deserving a special mention in this case (10). Retinal colour fundus imaging employing automated systems to detect the location of the optic disc, determining an appropriate region of interest (ROI), classifying vessels as arteries or veins, estimating vessel widths, and calculating the AVR have revealed **generalised arteriolar narrowing to be a definite biomarker** to detect damage caused to the retina and impending risks of systemic hypertension (3) (11).

Another important biomarker in identification of hypertension from retinal images is arteriovenous (AV) nicking that has been associated with both current and past histories of blood pressure (3).

Previous clinical studies have shown significant associations between **cerebral stroke** and the degree of retinal microvascular changes, such as arteriole narrowing and arteriovenous nicking (8) (12) (13). Going by the structural and functional similarities between retinal and cerebral vasculature, it is not difficult to comprehend such an association.

Chronic brain conditions are often caused by small-vessel ischaemia, or haemorrhage that lead to vascular infarcts and a loss of blood-supply to the brain (9). On one hand, with increasing age, there is arteriolar narrowing contributing extensively to hypertensive retinopathy, and presence of wider venules and loss of branching complexities in patients with lacunar (ischaemic) stroke, only highlight the relevance of a suboptimal retinal vascular network and retinal venular dilation as crucial biomarkers for risk stratification in stroke patients (3) (14).

On the other even after adjusting for other risk factors like age, sex, race, blood pressure and diabetes, the ARIC (Atherosclerosis Risk In Communities) study found retinal microvascular anomalies, AV nicking and focal retinal arteriolar narrowing to be associated with an increased risk of incident (including ischaemic) stroke as well as MRI-detected silent cerebral infarcts (White Matter Lesions/ WMLs), that contribute to sub-clinical stroke (3) (8).

The presence of both WMLs and retinopathy in fundus images has been associated with a larger risk of stroke than the absence of either finding, only indicating the severity of microvascular damage in such patients (15). Retinal lesions closely related to stroke are observed mostly in patients with a damaged blood-retinal barrier. Since the blood-brain barrier is analogous to the blood-retinal barrier, it can be implied that disruption of the cerebral microcirculation of the blood–brain barrier

may be an important pathophysiological feature in the occurrence of cerebrovascular disorders (3). Hence, retinal imaging not only highlights impending risks to the eye, but also stratifies their severity.

Cardiovascular Diseases

Owing to structural homology between retinal and cardiac vasculature, cardiovascular diseases can be found to be deeply linked to several ocular conditions. Arteriovenous nipping, narrowing of retinal arteries, and the dilatation of retinal veins have been shown to be important signs of increased cardiovascular risk (4). Cardiovascular diseases often manifest themselves as hypertension and atherosclerosis, fuelled by increasing age of an individual, irrespective of lifestyle and dietary modifications (3).

Fundus imaging helps shed light on systemic hypertension which reflects as dilation of blood vessels, formation of microaneurysms and severe damage to retinal vessel-walls. Similarly, the pressure in the dilated veins is often increased due to a dysregulation of venous outflow from the eye. Hence it is more of an action-reaction based phenomenon, closely interrelated to each other, which when detected with the help of imaging techniques, indicates a risk of impending CVD(4).

A deep correlation between the heart and the eye can also be deduced from the fact that the risk factors for arteriosclerosis, such as dyslipidaemia, diabetes, or systemic hypertension, are also risk factors for ocular conditions like retinal arterial or retinal vein occlusions, cataracts, age-related macular degeneration, and increased intraocular pressure (IOP). Fluctuation of IOP leads to unstable ocular blood flow and oxygen supply and subsequent oxidative stress – a key biomarker involved in the pathogenesis of glaucomatous neuropathy. Hence, if one monitors the growing modifications in the retinal microvasculature, closely enough, one can get an idea of the impending cardiovascular and cerebrovascular risks (4).

Popular clinical trials like the Beaver Damn Eye study and the Blue Mountain Eye Study have validated the fact that narrower arterioles and wider retinal venules predicted considerably higher risks of coronary heart disease (CHD) in moderately elderly population (16).

Tech giant Google's AI team has partnered with their health-tech subsidiary Verily to develop an algorithm to predict heart diseases faster and with the same accuracy as leading methodologies, with the help of retinal fundus images (17) (18).

One can legitimately conclude that digging a little deep into the eyes, gives away a clear picture of the heart, quite literally!

Diabetes

Diabetes is manifested when insulin production by the pancreatic beta cells becomes inadequate or the cells become insensitive to insulin, resulting in hyperglycemia. Diabetic retinopathy (DR) is touted to be one of the leading causes of blindness, globally. The early stages of DR, termed as non-proliferative DR are generally asymptomatic but close examination of the eye with the help of fundus and OCT images reveal early signs of damage like retinal ischaemia, exudates, microaneurysms, cotton-wool spots and haemorrhages (3). Retinal arteriolar calibre has been shown to widen with increasing glucose and HbA1C levels, which can also aid in DR risk stratification, in the early stages of DR as well (19).

Proliferative DR is indicated by wider retinal venular calibre and neovascularisation, which might lead to severe bleeding and permanent damage. Hence, early detection and risk stratification through retinal microvasculature examinations may prevent permanent damage in risk-prone diabetics (3).

Of late, deep learning and machine learning algorithms are being coupled with imaging techniques to enhance specificity of diagnosis and increase efficacy of treatment and management of DR (20).

Neurodegenerative Diseases

Major neurodegenerative diseases like **Alzheimer's Disease (AD)**, **Parkinson's Disease (PD)** and **Multiple Sclerosis (MS)** are deemed as incurable owing to their progressive nature and limited efficacies of their respective treatment regimens. Since most of the treatment measures focus on reducing the impact of symptoms rather than treating the root cause, mostly due to our limited understanding of the causes and early developmental signs of these conditions, it is strongly recommended to develop easy, non-invasive, monitoring tools for early screening and detection of these diseases, trace their progression and assess the efficacy of subsequent treatment interventions (3).

OCT scanning to detect retinal vascular changes has been established as a relatively non-invasive and well-accepted imaging method among physicians and patients alike. With embryological, structural and functional similarities between retinal blood vessels and those in the brain, a relatable estimate of the progress of damage to brain vasculature can be made by closely observing retinopathic phenomena.

Different forms of disabilities faced by MS patients, like numbness, tingling, visual impairment, fatigue, weakness and bladder function disturbance are caused by nerve-cell disintegration. Retinal vasculitis has been stated as a common consequence of MS as well (21) (22). MRI scans have been the conventional choice of scanning through WMLs to trace evidences of MS progression. Clinical studies have

now backed the efficacy of substituting MRI scans with OCT scans to determine similarities between changes in retinal nerve fibres and vasculature and those in MRI-detected brain tissue, and monitor the progress of degeneration thereby (23). OCT also scans the RNFL and adjacent ganglion cell layer (GCL) thickness effectively in MS patients, with or without optic neuritis (ON) and the same has been detected to be thinner than normal controls. RNFL thickness has also been linked to brain atrophy in MS patients (3).

Since progressive neurodegenration, β-amyloid plaque deposits, small-vessel disease and microvascular insults are common pathologic characteristics of diabetic retinopathy, glaucoma, dementia (AD) as well as age-related macular degeneration (AMD), an impending risk of AD can be detected when the other conditions are detected, and they need not be affected by old-age among patients (24). Clinical trials have indicated microvascular retinopathy to be directly related to cognitive decline, which further strengthens this argument. Clinical trials using fundus imaging have also backed the link between reduced branching complexities, narrowed venular diameters and reduced vessel tortuosity among AD patients, indicating cognitive decline (AD) in patients and effectively differentiating from vascular dementia that is indicated by increasing venule diameter (25).

Artificial intelligence, a gift of modern-day technology, is now being implemented to detect AD using a sophisticated camera and retinal imaging approach to monitor early signs. This has been achieved by locating deposits of β-amyloid plaques in clusters which seem to be more abundant in certain regions then others in the human retina, in early stages of the condition (26).

A pilot study in New York, assessed the differences in RNFL, inner retinal layer and macular thickness between healthy controls and PD patients, using OCT scanning and found a considerable difference in only macular thickness (3).

Another Korean study related retinal thinning and dopaminergic deterioration in the brain using OCT imaging coupled with microperimetry, a specialised visual-field test. The study revealed a significant relationship between retinal thickness and the dopamine transporter density in the left side of the basal ganglia (substantia nigra) region of the brain(27).

Inflammation & Cancer

Systemic **inflammation** often manifests itself in the eyes in the form of uveitis. Chronic inflammatory diseases like **Inflammatory Bowel Disease (IBD)** and **Rheumatoid Arthritis (RA)** have also shown significant symptoms of ocular manifestations, in the form of keratoconjunctivitis sicca (dry-eye syndrome), episcleritis, scleritis , corneal changes, and retinal vasculitus (5) (28) (29) (30). Though most of these manifestations might be secondary, they can still predict risks

of further inflammation and confirm active conditions that demand immediate treatment.

Implementing artificial intelligence algorithms and coupling them with modern scanning methods, researchers at the University of Washington have developed an app called **BiliScreen** which assesses the amount of bilirubin present in a patient's eye to predict an incumbent risk of pancreatic cancer. A clinical study involving 70 participants, found that Biliscreen had a sensitivity of almost 90%. Though it needs a VR box to obtain high quality images with zero noise and disturbance, future versions of the app can be expected to require nothing but the photographing capacity of the patient. This app could potentially be useful in detecting hepatitis as well (31).

An Emerging Trend in Non-invasive Biomarkers : Tear Proteomics

A large number of longitudinal studies are being conducted internationally to assess the efficacy and accuracy of non-invasive techniques in predicting the diagnostic and prognostic information for most chronic diseases, at their earliest, curable stages. Apart from imaging analysis, automated mass-spectrometry and bio-informatics, proteomics is another extremely powerful, emerging tool to generate information on a molecular (genomic) level and produce high-throughput biomarker data (3) (32) (33).

The human tear is a protein-rich biological mixture concerned with the lubrication of vital parts of the ocular anatomy, containing immune-protective properties to keep the eyes safe from environmental and pathological threats, supplying nutrition to the cornea and modulating several optical properties. Tear composition analysis, enhanced over the past decade owing to advances in mass spectrometry, metabolomics, glycomics and lipidomics technologies, has made it convenient to assess the physiological condition of the underlying tissues (32) (34).

Not only is tear fluid easier to collect compared to other invasive techniques used in blood-biomarker detection or tissue-sampling for biopsies, the concentration of proteins (be it disease-biomarkers or healthy ones) is more compared to blood. One need not worry about sample purification and concentration while performing diagnostic analysis. Comparing healthy control biomarkers and analysing them against diseased ones are making it easier to detect not only ophthalmological anomalies but have also shown immense potential in chronic and progressive diseases like AD, PD, breast cancer and pancreatic cancer, to name a few (32) (35) (36). Personalized medicine could be one of the biggest gainers in this business, owing to the accuracy presented by tear-proteomic research.

Conclusion

Early detection techniques, that too non-invasive and economical like retinal scanning and analysis, would enhance patient adherence, increase patient benefit and reduce healthcare costs exponentially. Patient reported outcomes can then be used effectively to monitor treatment regiments on a two-way basis, instead of physicians merely recommending medicines within a defined course of action.

In the long run, retinal scanning and imaging analysis would lead to big datasets from different patient pools which when compiled and compared, are bound to give rise to even bigger sets of cross-linked data. Such mammoth datasets when fed into computer algorithms to be coupled with the increasingly popular AI technologies, are most likely to find innovative and valued applications when mined to influence high-level technologies like those currently being used in genomics and bio-informatics.

With huge datasets to manage along with their unique (scientific / medical / genomic) components to be mapped and linked, there would be ample job opportunities for interdisciplinary teams who have to decipher borderline information from ophthalmology, neurology, genomics and information technology and create scope for further researchers to dig deeper into the microvascular dynamics of the brain, retina and other major, interconnected organs and solve some of the existing paradoxes of the human body. Considering AI has already posed threats to human-based jobs, this could be an effective way to counter such adversities and increase human productivity in the long run.

Summing it up, one can term retinal image analysis as a comprehensive imaging tool with huge potential to predict the prognostic and diagnostic information with impeccable accuracy by integrating structural and functional data sets and longitudinally mapping the natural course of the disease.

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