INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe impairment of visual function in people older than 50 years of age in industrialized countries.[1] Choroidal neovascularization (CNV), the hallmark of 'wet' or 'neovascular' AMD, is responsible for approximately 90% of cases of AMD associated severe vision loss .[2]

The disease has a profound effect on quality of life of affected individuals and represents a major socioeconomic challenge due to the expected increase in life expectancy. Vascular endothelial growth factor (VEGF) has been identified as an important pathophysiological player in neovascular AMD and intraocular inhibition of VEGF is one of the most efficient therapies in medicine. However, the therapeutic benefit is accompanied by significant economic investments. The burden of disease has turned into a burden of care.[3]

A ground-breaking innovation in diagnostic technologies, such as optical coherence tomography, allows high-resolution visualisation of disease morphology and provides a promising horizon for early disease detection and efficient therapeutic follow-up. However, definite conclusions from morphologic parameters are still lacking, and valid biomarkers have yet to be identified to provide a practical base for disease management.[3]

Choroidal structure is of particular interest in AMD because abnormalities of the choroidal circulation have been hypothesized to contribute to the development of AMD.[4] A strong correlation exists between ageing and choroidal thinning, most likely due to progressive loss of tissue and vascular narrowing.[5] This process, along with the reduced Bruch's membrane permeability that is found with increasing age, impairs the oxygen supply to the retina.[6]

Retinal pigment epithelial cells release vascular endothelial growth factor (VEGF) to dilate the choroidal vessels and increase the blood flow, but this may also lead to the development of choroidal neovascularization (CNV).[7] The association of intraocular VEGF levels and choroidal blood flow is further supported by the choroidal thinning that is detected in eyes receiving intravitreal anti-VEGF therapy for neovascular age-related macular degeneration (nAMD).[8,9]

Therefore, choroidal thickening is hypothesized to occur in the active phase of nAMD due to increased levels of VEGF and other proinflammatory factors together with hydrostatic variation in the blood flow within the newly formed vessels.[10]

Fluorescein angiography (FA) is the gold standard for diagnosis of CNV and has been used to quantify areas of CNV. However, fluorescein dye leaks from blood vessels, making it less ideal for visualization of details in the

choroidal circulation. In contrast to fluorescein, Indocyanine green (ICG) allows for more detailed visualization of choroidal vascular patterns. [11] However, both do not provide cross-sectional anatomical information and are unable to accurately identify the depth of vascular pathology.[12]These methods are also invasive because of the need for contrast dye, which has the potential to induce anaphylactic reaction.[13]

Several noninvasive methods to visualize choroidal blood flow have been developed such as; Doppler Optical coherence tomography (OCT), and Laser Doppler flowmetry for subfoveal choroidal circulation.[12] Magnetic resonance imaging (MRI) is another noninvasive imaging modality that can provide structural, physiological, and functional information on the choroid. However, it is more expensive and lacks in spatial resolution, allowing only 3 layers of the retina/choroid complex to be discriminated.[14]

The development of spectral domain optical coherence tomography (SD-OCT) in 2002 provided faster and higher resolution imaging, allowing additional layers in the retina to be discerned. In 2008, **Spaide** developed a technique called Enhanced depth imaging technique using SD-OCT (referred to as EDI-OCT). This is achieved simply by moving the SD-OCT device closer to the eye to invert the image, such that the zero-phase delay line is positioned at the choroidal side

of the image frame.[15] which led to the ability to distinguish layers in the outer choroid and sclera.

The advent of EDI-OCT imaging of the choroid has enabled new directions in research relating to the normal and pathological roles of the choroid. There are much data confirming that abnormalities in choroidal structure and function contribute to major ocular diseases and patterns of choroidal thickness variation may be observed in certain disease states, including AMD, and may be influenced by treatment. However, it is not clear whether these variations are a contributing factor or a consequence of disease.[16]

AIM OF THE WORK

We aim to study the correlation between choroidal thickness, and the activity of choroidal neovascularization in cases of neovascular (wet) Age related macular degeneration using Spectral domain Ocular coherence tomography.

AGE RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is referred to as the leading cause of severe and irreversible visual loss worldwide. The disease has a profound effect on quality of life of affected individuals and represents a major socioeconomic challenge.[3]

Prevalence of Age-related macular degeneration

The prevalence of AMD among 40 to 49 year olds is 2.1%, which increases dramatically to 35% among those over 80 years of age. Additionally, the disease can progress with approximately 10%–20% of patients with dry AMD progressing to the exudative / wet / neovascular form. Furthermore, almost 40% of patients have bilateral disease.[17]

Approximately 11 million individuals have AMD in the United States (U.S.) alone, with a global prevalence of 170 million. AMD is thereby the leading cause of visual disability in the industrialized world and the third leading cause globally. Aging is the greatest risk factor; that's why; the prevalence of AMD in the U.S. is anticipated to increase to 22 million by the year 2050, while the global prevalence is expected to increase to 288 million by the year 2040.[18]

In a cross sectional survey conducted by department of ophthalmology, Alexandria University, The overall prevalence of AMD was 6.6%. The prevalence of early and

late AMD was 5.3 and 2.4%, respectively. There was a significantly higher prevalence of early and late AMD among those aged more than 75 years as compared with other age groups. The prevalence of AMD was 9.2% among male participants compared with only 4.1% among female participants. A significantly higher percentage of patients were diagnosed with AMD among those with a history of systemic hypertension (12.1%) than among those without hypertension. [19]

Classification of AMD

There are many classifications of AMD. The most commonly used classification is that of Age Related Eye Disease study (AREDS) designed to assess the natural course and risk factors for age-related cataract and AMD, and the effects of antioxidant vitamins and minerals on these two ocular conditions.[20] According to this study, and as shown in figure (1), AMD is classified as follow;

- ***No AMD*** **(AREDS category 1)**: it is characterized by no or few small drusen (<63 µm in diameter).
- ***Early AMD*** **(AREDS category 2)**: is characterized by a combination of multiple small drusen, few intermediate drusen (63–124 µm in diameter), or mild retinal pigment epithelium (RPE) abnormalities.
- ***Intermediate AMD*** **(AREDS category 3)** is characterized by any of the following features:

(1) Numerous intermediate drusen.
(2) At least one large druse (125 µm or larger in diameter).
(3) Geographic atrophy (a sharply demarcated, usually round or oval, area of atrophy of the RPE not involving the center of the fovea)

- ***Advanced AMD* (AREDS category 4)** is characterized by one or more of the following (in the absence of other causes) in one eye:

(1) Geographic atrophy of the RPE involving the foveal center.
(2) Neovascular maculopathy that includes the following:

- Choroidal neovascularization (CNV) defined as pathologic angiogenesis originating from the choroidal vasculature that extends through a defect in Bruch's membrane.
- Serous and/or hemorrhagic detachment of the neurosensory retina or RPE.
- Retinal hard exudates (a secondary phenomenon resulting from chronic intravascular leakage).
- Subretinal and sub-RPE fibrovascular proliferation.
- Disciform scar (subretinal fibrosis).[20]

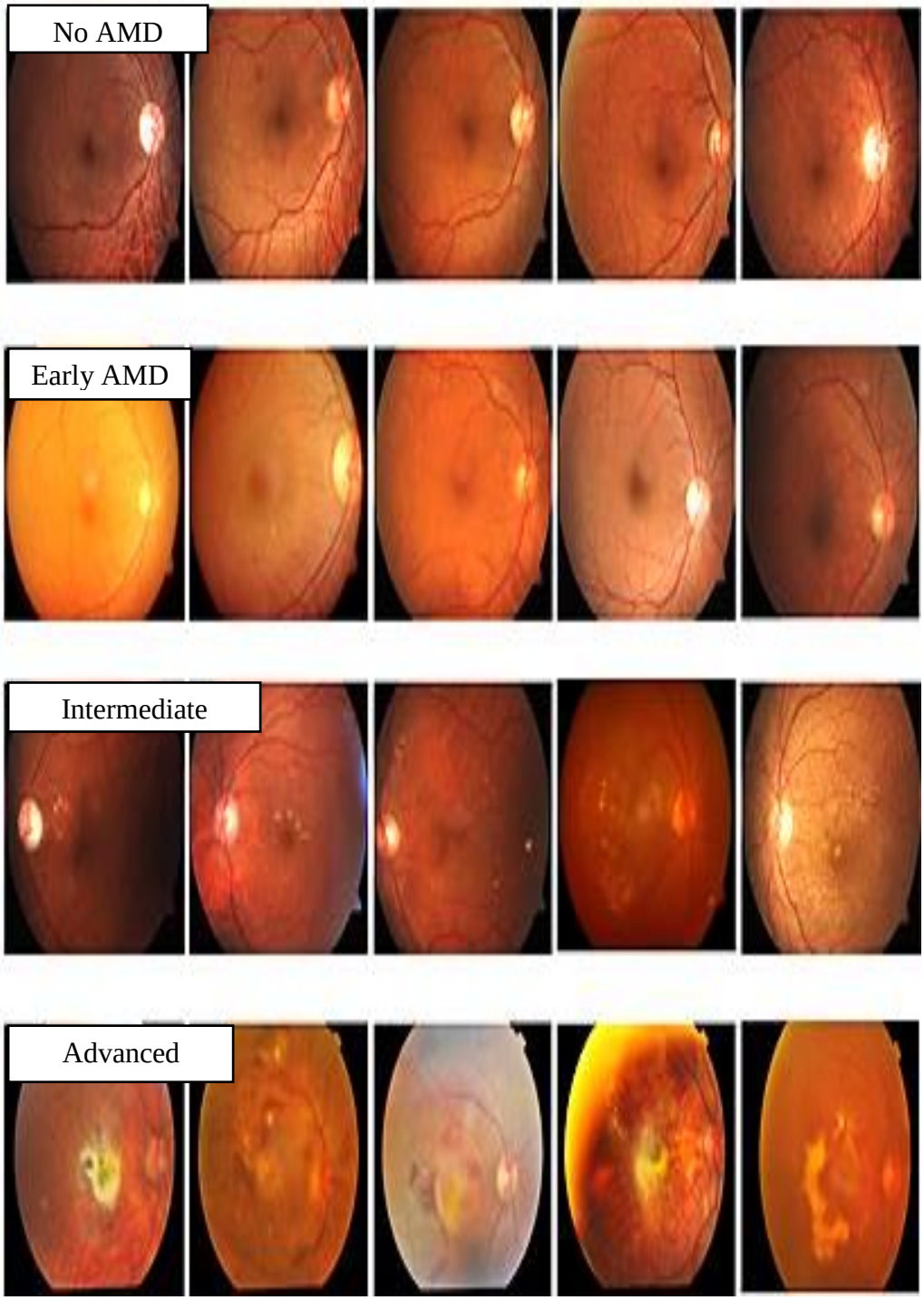

Figure (1): AMD stages according to AREDS.[21]

Risk factors:

Risk factors for AMD include ethnicity, gender, genetics, diet, alcohol consumption and sunlight exposure. It has been shown that the late stages of AMD are more common in whites than in other ethnic groups and that women are affected more than men. Nevertheless, the strongest, most consistent risk factors are smoking and age.[22]

Modifiable risk factors:

- ***Smoking:***

  In **the Blue Mountains Eye Study**, current smoking was associated with an increased risk of geographic atrophy and late AMD.

  In **the Rotterdam Study**, current smoking was associated with an increased risk of incidence of geographic atrophy, neovascular AMD, and late AMD; past smoking was associated with an increased risk of incidence of neovascular AMD and late AMD.[23]

- ***Total serum cholesterol:***

In **the Beaver Dam Eye Study**, total serum cholesterol was inversely associated with incidence of neovascular AMD. While in **the Blue Mountains Eye Study**, increased total serum cholesterol, having diabetes, and older age at menopause were positively associated with incidence of geographic atrophy; and an increase in high-

density lipoprotein serum cholesterol was inversely related to incidence of geographic atrophy.[23]

- ***Alcohol consumption:***

The epidemiologic data on the association of AMD with alcohol consumption is inconsistent.[24]

In **the Beaver Dam Eye Study**, there was an association with retinal drusen in men and beer drinking (seven drinks per week), but none in women.[25]

In **the Blue Mountains Eye Study**, there was no association found, and in **the National Health and Nutrition Examination Survey I**, wine consumption was reported to be protective leading to a 34% reduction in relative risk. It is presumed that antioxidant phenolic compounds found in high concentrations in red wine may explain their finding.[26]

However, it similarly has been shown to increase oxidative stress or to modify the mechanisms that protect against oxidative stress, so it is hypothesized that alcohol may have a J-shaped effect on AMD risk: protective for AMD when consumed in moderate amounts and associated with an increased risk with heavier consumption.[27]

- ***Exercise:***

Different studies show regular physical activity correlate to lower incidence of exudative AMD.[28] In **the Beaver Dam Eye study**, persons with an active lifestyle (defined as regular activity three or more times a week) were found 70% less likely to develop neovascular AMD; an

increased number of metres walked per day decreased the risk of exudative AMD by 30%.[29] This can be explained as the result of lowering systolic blood pressure, lowering white blood cell count, and decreasing body mass index.[24]

Non-modifiable risk factors:

- **Genes associated with development of AMD**

Major progress has been made in identifying genetic susceptibility variants for AMD. Variants at chromosome 1q32 (in the region of complement factor H) and 10q26 (LOC387715/ARMS2) account for a large part of the genetic risk to AMD. That was validated in numerous studies.[30]

In addition, several susceptibility variants at other loci make contribution to genetic risk for AMD; among these, multiple studies support the role of variants in APOE and C2/BF genes.[30]

Genome-wide association and re-sequencing projects, together with gene-environment interaction studies, are expected to further define the causal relationships that connect genetic variants to AMD pathogenesis and should assist in better design of prevention and intervention.[30]

Siblings of individuals with AMD have three to six-fold higher risk of disease compared to individuals from the population at large.[31] Individually, the genetic variants at the chromosome 1q32 (CFH) and 10q26 (LOC387715/ARMS2) regions correspond to an increase in risk to siblings of only ~1.2 to 1.6-fold.[32]

Pathogenesis of AMD;

Although aging will not inevitably lead to AMD development, there are changes with age that can predispose the eye to development of AMD. However, the exact molecular causes of AMD pathogenesis remain unclear. Although candidate gene, genome-wide association studies, and epidemiological studies have implicated the lipid metabolism-cholesterol pathway in AMD pathophysiology, the role is unclear and at times inconsistent.[33]

The vascular theory, suggested by **Friedman**, states that with increased resistance in the choroidal vessels, there is an increase in the osmotic gradient against which the retinal pigment epithelial cells must pump. This leads to retinal pigment epithelial cell dysfunction and the accumulation of metabolic debris and drusen formation. Furthermore, the decrease in choroidal perfusion causes ischemic/hypoxic injury and increased oxidative stress, which can signal choroidal neovascularization formation.[34]In 1994, **Ramrattan and his associates,** reported progressive decrease in the thickness of the choroid from 193 μm in the first decade of life to 84 μm in the 10th decade. There is also a 45% decrease in choriocapillary density and a 34% decrease in the lumen diameter of the choriocapillaries with advancing age.[35]These changes support **Friedman[34]** theory in decreasing choroidal perfusion.

On the other hand, in the nonvascular theory, old retinal pigment epithelial cells can lead to retinal pigment epithelial cell dysfunction, which in turn can cause choriocapillary atrophy over time, in addition to individual's genetic predisposition and environmental stressors in the setting of structural and vascular changes make the eye more susceptible to AMD development.[36]

Bhutto L & Lutty G suggested that there is a mutualistic symbiotic relationship between the components of the photoreceptor/retinal pigment epithelium (RPE)/ Bruch's membrane /choriocapillaries complex that is lost in AMD. Which component in this complex is affected first appears to depend on the type of AMD.[6]

In atrophic AMD, it appears that large confluent drusen formation and hyperpigmentation (presumably dysfunction in RPE) are the initial insult and the resorption of these drusen and loss of RPE (in the form of hypopigmentation) can be predictive for progression of geographic atrophy (GA). The death and dysfunction of photoreceptors and choriocapillaries appear to be secondary events to loss in RPE. In neovascular AMD, the loss of choroidal vasculature presumably the initial insult to the complex. Loss of choriocapillaries with an intact RPE monolayer in wet AMD has been noted.[6]

Inflammatory biomarkers:

Several immunological molecules, complement factors and inflammatory mediators have been identified at the site of AMD lesions.[37] In fact, chronic inflammation appears to be a causative factor for the development of AMD by causing endothelial dysfunction and facilitating interactions between modified lipoproteins, monocyte-derived macrophages, T-cells and normal cellular elements of the retinal vasculature. Activated macrophages and microglia may cause cellular damage, Bruch's membrane degradation and angiogenesis by secreting chemokines and cytokines.[38] Using electron microscopy or immunohistochemistry methods, macrophages can be found in the area of geographic atrophy phagocytising pigment debris[39] and around CNV in wet AMD.[40]

Several markers of systemic inflammation have been studied. One of them is C-reactive protein (CRP), an acute phase serum protein, and a surrogate for interleukin-6 (IL-6). It directly upregulates endothelial cell adhesion molecules and promotes the release of chemo-attractant chemokine, which have a negative effect on the retinal microvasculature.[38]

Hong and colleagues in their systematic review summarize the currently available evidence from clinic-based and population-based studies investigating this association.