# INTRODUCTION

Age-related macular degeneration (AMD) is a debilitating disease on central vision in patients over 50 years old. It was first described as a symmetrical central chorioretinal disease occurring in senile individuals. It was not until 1980 that AMD was described as a significant cause of blindness in the United States. In 2004, the World Health Organization estimated that there are 14 million individuals worldwide suffering from blindness or are severely visually impaired due to AMD ***(Chiou., 2011)***.

Worldwide about 30 million people in the year 2010 were affected by the disease. Especially, the prevalence and incidence of AMD is increasing in individuals older than 50 years old ***(Hasler and Flammer., 2010)***.

AMD is the leading cause of irreversible central vision loss in developed countries. Prevalence data suggest that AMD will affect more than 3 million people in the United States by 2020, while there are 1.75 million patients in the year 2013. With the aging of populations, not only in the United States but also globally, AMD will become an increasingly prevalent and important condition worldwide ***(Ferris et al., 2013)***.

As the population in the western world is growing older, the incidence of losing the ability to read and to drive due to AMD is becoming increasingly apparent. An analysis in 2004

reported that among Americans over the age of 40 years, AMD and/or geographic atrophy were present in at least one eye in 1.5% of the population. Given the enormous impact of AMD on the aging population, much public attention and research has been focused on this condition in the past decade ***(Chiou., 2011).***

AMD affects the macula. The fovea lies at the center of the macula and is approximately 2 mm in diameter. The fovea contains the highest density of cone photoreceptor cells and is the only region of the retina where 20/20 vision is attainable. Thus, lesions developing in this region can have a major impact on visual function ***(Berman and Brodaty., 2006)***.

There have been significant advances in the clinical management of patients with AMD. The clinical workload associated with the frequent follow-up required is substantial. Furthermore, as more new patients are diagnosed and the population continues to age, the patient population will continue to increase. It is thus vital that clinical services continue to adapt so that they can provide a fast and efficient service for patients with neovascular AMD ***(Freeman et al., 2012)***.

# AIM OF THE WORK

The aim of this work was to study if the regimen of 3 successive intravitreal Injection of Ranibizumab can cause complete cure of CNV in AMD or not.

# DEFINITION AND CLASSIFICATION

Age-related macular degeneration (AMD), also known as age-related maculopathy (ARM), is a common, chronic, progressive degenerative disorder of the macula that affects older individuals and features loss of central vision as a result of abnormalities in the photoreceptor/retinal pigment epithelium (RPE)/Bruch's membrane/choroidal complex often resulting in geographic atrophy and/or neovascularization. It is characterized by the presence of specific clinical findings including drusen and RPE changes as early features with no evidence the signs are secondary to another disorder ***(Yanoff and Duker., 2014)***.

**Classification**

Currently, several AMD classification schemes, grading systems, and severity scales have been developed in an effort to provide standards to assist clinicians and researchers in the diagnosis and management of this important disorder. Most of these have been based on standardized grading of color fundus photographs and some have been considered to be potentially useful for clinical work. There is at present no universally accepted precise definition, including both initial diagnosis and staging, of the AMD phenotype for either clinical or research purposes. There is not even consensus on basic terminology, with some groups using AMD and others using age-related maculopathy or ARM or ARMD. Furthermore, terms such as

early and intermediate have different meanings in various classification systems. Finally, there may be a variety of entities worldwide that are termed AMD, but that have differing progression characteristics associated with dissimilar causes and risk factors (genetic and phenotypic) ***(Ferris et al., 2013)***.

**Conventionally**, AMD has been divided into two main types:

- **Dry (non-exudative, non-neovascular) AMD** is the most common form, comprising around 90% of diagnosed disease. Geographic atrophy is the advanced stage of dry AMD; it has been authoritatively suggested that the term 'dry AMD' be used only to describe Geographic atrophy rather than earlier stages of AMD.

- **Wet (exudative, neovascular) AMD** is much less common than dry, but is associated with more rapid progression to advanced sight loss. The main manifestations are Choroidal neovascularization (CNV) and Pigment epithelial detachment (PED), though in recent years at least two additional conditions, retinal angiomatous proliferation (RAP) and polypoidal choroidal vasculopathy (PCV), have been included under the umbrella of neovascular AMD by many authorities ***(Kanski and Bowling., 2015)***.

***Ferris et al. (2013)*** Proposed a clinical classification for AMD based on fundus lesions assessed within 2 disc diameters of the fovea in persons older than 55 years. The AMD classification system proposed focuses on the clinical phenotype associated with the development of large drusen and

pigmentary abnormalities leading to neovascular AMD, Geographic atrophy, or both.

**Table (1):** Clinical classification for AMD ***(Ferris et al., 2013)***.

| Classification of AMD | Definition (lesions assessed within 2 disc diameters of fovea in either eye) |
|---|---|
| No apparent aging changes | No drusen and No AMD pigmentary abnormalities* |
| Normal aging changes | Only drupelets (small drusen ≤ 63 μm) and No AMD pigmentary abnormalities* |
| Early AMD | Medium drusen >63 μm and ≤125 μm and No AMD pigmentary abnormalities* |
| Intermediate AMD | Large drusen >125 μm and/or Any AMD pigmentary abnormalities* |
| Late AMD | Neovascular AMD and/or Any geographic atrophy |

*AMD pigmentary abnormalities: any definite hyper-or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

# ANATOMY OF THE RETINA

**Layers of the retina**

The retina consists of 10 layers which are actually a remarkable organization of alternate groupings of the retinal neurons and their processes (Fig. 1):

1. Retinal pigment epithelium (RPE)
2. Photoreceptor cell layer
3. External limiting membrane
4. Outer nuclear layer
5. Outer plexiform layer
6. Inner nuclear layer
7. Inner plexiform layer
8. Ganglion cell layer
9. Nerve fiber layer
10. Internal limiting membrane (ILM)

***(VanPutte et al., 2014)***

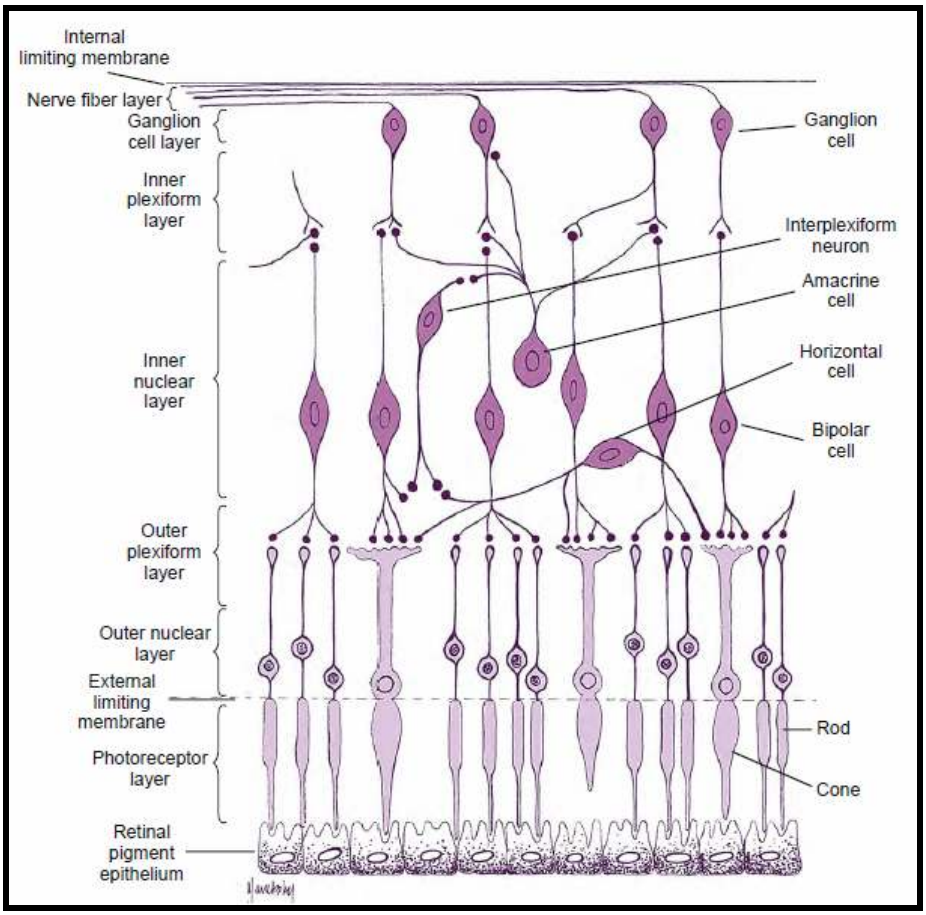


**Figure (1):** Retinal cells and synapses. The 10 retinal layers are indicated ***(VanPutte et al., 2014)***.

## *Macula Lutea*

The macula lutea appears as a darkened region in the central retina and may seem to have a yellow hue because of the xanthophyll pigments, lutein, and zeaxanthin. These pigments are located throughout the retina, but the greatest concentration is in the macula. These pigments apparently act

as filters, absorbing short wavelength visible light to reduce chromatic aberration but may also have an antioxidant effect, suggesting a protective role against Ultraviolet radiation damage ***(Patton and Thibodeau., 2013)***.

The macula lutea is approximately 5.5 mm in diameter; its center is approximately 3.5 mm lateral to the edge of the disc and approximately 1 mm inferior to the center of the disc. The pigment epithelial cells are taller and contain more pigment than cells elsewhere in the retina, contributing to the darkness of this area. The choroidal capillary bed also is thicker in the macula lutea than elsewhere.The entire macular region consists of the foveola, the fovea, and the parafoveal and perifoveal areas (both are annular regions) (Fig. 2). These areas are described and delineated on the basis of histologic findings, with consideration given to the number and rows of cells in the nuclear layers ***(Picaud., 2003)***.

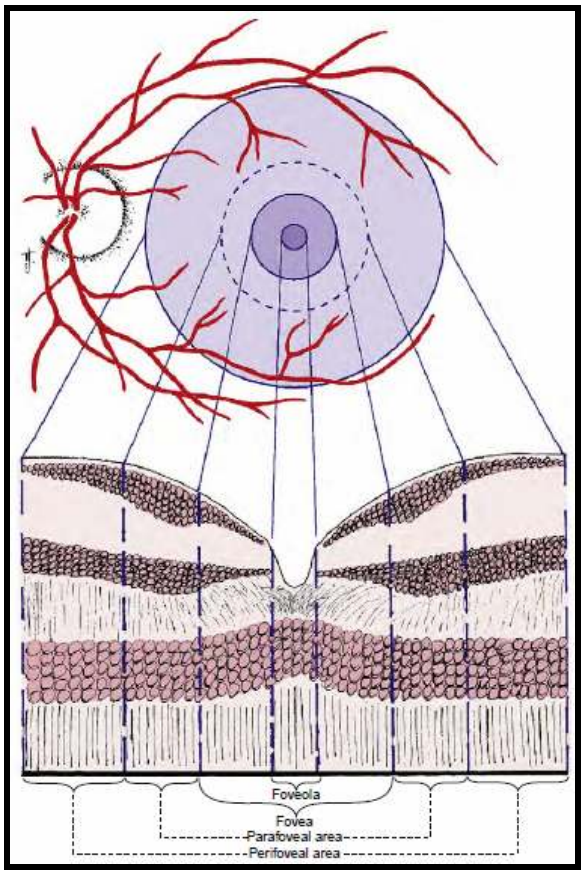


**Figure (2):** Schematic showing regions of retina and corresponding histologic architecture ***(VanPutte et al., 2014)***.

## Clinical Comment: Terminology

The terms used to describe the macular area differ between the histologist and the clinician. The histologist uses the word fovea to describe what a clinician would name macula, and the histologist calls the foveola that which a clinician would name the fovea. The term macula is purely a clinical one and usually refers to the area of darker coloration

that is approximately the same size as the optic disc; clinically, the term fovea then refers to the very center of this area. The posterior pole is another term used in clinical descriptions of the fundus. There is no universal agreement regarding its definition, and its usage varies from clinician to clinician ***(Yanoff and Sassani., 2015)***.

***Fovea (Fovea Centralis)***

The shallow depression in the center of the macular region and is formed because the retinal neurons are displaced, leaving only photoreceptors in the center. The fovea has a horizontal diameter of approximately 1.5 mm. The curved wall of the depression is known as the *clivus*. The fovea has the highest concentration of cones in the retina. The ratio between cone cells and ganglion cells approaches 1:1 ***(Forrester et al., 2015)***.

Within the fovea is a capillary-free zone 0.4 to 0.5 mm in diameter. The lack of blood vessels in this region allows light to pass unobstructed into the photoreceptor outer segment. The only photoreceptors located in the center of the fovea are cones. The external limiting membrane is displaced vitreally because of the lengthening of the outer segments. Most of the other retinal elements are displaced, allowing light to reach the photoreceptors directly without interference of other retinal cells ***(Ahnelt., 1998)***.

The cells of the inner nuclear layer and ganglion cell layer are displaced laterally and accumulate on the walls of the fovea. The photoreceptor axons become longer as they deviate away from the center; these fibers are called Henle's fibers. They must take an oblique course to reach the displaced bipolar and horizontal cells (Fig. 3). This region of the outer plexiform layer is known as Henle's fiber layer. The retinal layers and the foveal indentation are clinically evident with an Ocular coherence tomography (OCT) view of the retina (Fig. 4) ***(Duker et al., 2014)***.

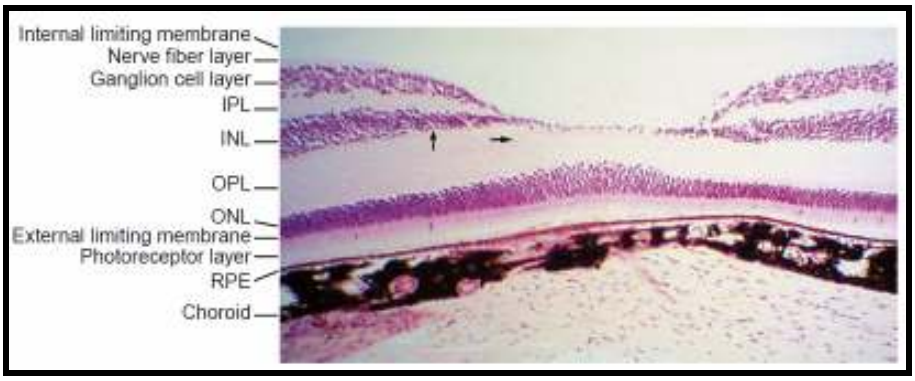


**Figure (3):** Light micrograph of foveal region. Layers present in the center of the foveal area are RPE, photoreceptor layer, external limiting membrane, outer nuclear layer, Henle fiber layer (note oblique orientation of fibers at heavy arrow), a few scattered nuclei from inner nuclear layer, ILM. Light arrow shows middle limiting membrane within outer plexiform layer ***(Yanoff and Sassani., 2015).***

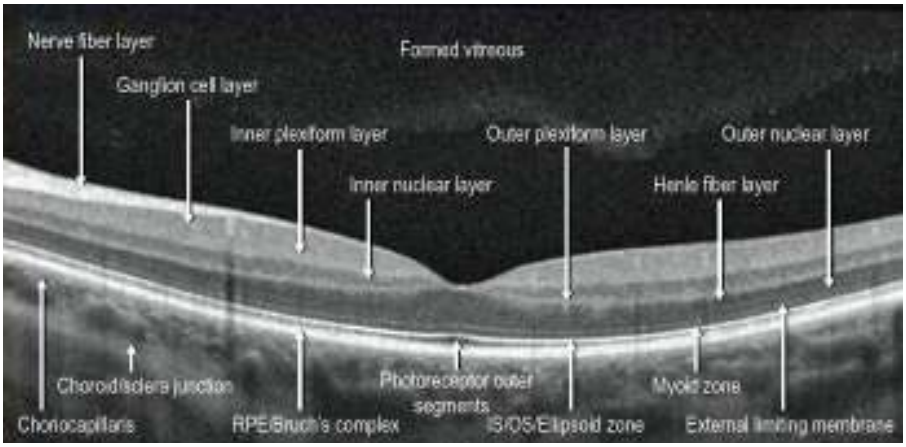


**Figure (4):** OCT scan of left macular area, retinal layers can be visualized; foveal indentation clearly evident ***(Duker et al., 2014)***.

### *Foveola*

The diameter of the foveola is approximately 0.35 mm. At the foveola, the retina is approximately 0.13 mm thick, compared with 0.18 mm at the equator and 0.11 mm at the ora serrata.1 The foveola contains the densest population of cones that have the smallest cross-sectional diameters of all the photoreceptors. The layers present in the foveola are the (1) RPE, (2) photoreceptor layer, (3) external limiting membrane, (4) Outer nuclear layer (which contains about 10 rows of cone nuclei), (5) Henle's fiber layer, and (6) the ILM ***(Forrester et al., 2015)***.

### *Parafoveal and Perifoveal Areas*

The annular zone surrounding the fovea can be divided into an inner parafoveal area and an outer perifoveal. The width