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Diabetic Retinopathy: Lakatosian Analysis from the Perspective of Medical Bioengineering

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Abstract: *Diabetic retinopathy is a microvascular complication of diabetes mellitus, which has a high social cost and requires the intervention of the Medical Bioengineer. This is the reason why the epistemological analysis of emerging trends in the study of diabetic retinopathy is carried out to characterize problematic fields and epistemic matrices that make it possible to integrate an understanding horizon from the field of Medical Bioengineering. The study included three stages: construction of the thematic field; characterization of the elements of the methodology of scientific research programs (hard core, protective belt and heuristics); and reconstruction of the problematic field. The pathogenic and pathophysiological theories that make possible to understand the methods, models and technological tools developed by the Medical Bioengineer are analyzed. The problem field is developed at the disciplinary level (biomedical, clinical, transdisciplinary approach of medical bioengineering), the natural history of the disease (pre-pathogenic, pathogenic, post-pathogenic periods), prevention levels (primary, secondary, tertiary and quaternary), in addition to the philosophical field (ontological, ethical, epistemological). It is concluded that the research of diabetic retinopathy in the field of Medical Bioengineering is developed as a research program of the Lakatosian type, oriented to the development of processes, products, services and devices oriented to patient care.*

Keywords: *biomedical engineering, diabetes mellitus, diabetic retinopathy, epistemology, philosophy of science*

I. Introduction

Currently, medical sciences are facing the exponential increase of chronic and degenerative diseases, which require the intervention of multidisciplinary teams to meet the health needs and improve the quality of life of these patients. Among the members of the health team to care for the patient is the Medical Bioengineer. When establishing the level of participation in patient care, what is the role played by the Medical Bioengineer? The questioning is of a practical nature, but underlies the question an epistemological sense related to the delimitation of professional fields, but it is also linked to disciplinary areas of the sciences that contribute to patient care, in an exercise of reconstructing the care environment where the patient is at the center. To explore this question, two paths can be followed. One goes directly to philosophical reflection. The other, makes it possible to situate oneself in the world of life, select a practical problem and lead reflection towards the characterization of problematic fields, in which the Medical Bioengineer performs professionally, academically and scientifically.

It is on this path that reflection arises linked to the medical application of robotics [1] and nanotechnology [2] that are changing the positivist scientific discourse towards a meta-narrative that aims to transform the health/disease/care relationship [3], as is happening with the development of medicine translational [4] and the emergence of medicine centered on the patient [5]. Meta-narratives that arise with foundations that seek to articulate and give coherence to scientific theories with the natural history of the disease and thus promote a holistic and comprehensive medicine [6].

It is not possible to deny the influence of model design based on the knowledge generated by Medical Bioengineering, recognizing the importance of establishing complex and non-linear mathematical algorithms that allow the intervention of the physician in the different levels of medical care [7]. Traditionally, the doctor is expected to develop in the first level of care, related to the promotion of health and specific protection [8]. However, it is forgotten on a daily basis that prevention and protection is also carried out when the disease has been installed in the patient. In this stage of the natural history of the disease, the prevention and protection of health is aimed at preventing or delaying the onset of complications, sequelae of the disease, disability and even death.

In this order of ideas, diabetes mellitus (DM) in general, and diabetic retinopathy (DR) in particular, is shown as a paradigmatic and cutting-edge model for the epistemological analysis that opens up horizons to the conception of the pragmatic task of the Medical Bioengineer; therefore, what is the importance of DR for the Medical Bioengineer?

1.1. Relevance of the DR for the Medical Bioengineer

DM is a chronic and multifactorial disease, which occurs when the pancreas does not produce enough insulin or there is tissue resistance to it, causing the homeostatic balance of glucose is altered, and consequently, the patient is in a state permanent hyperglycemia [9]. It is linked to risk factors associated with lifestyle and obesity. In the last 10 years it has emerged as a global pandemic [10]. In 2017 it affected 451 million people in the age range of 18 to 99 years and it is estimated that by 2045, the world population with DM will reach 693 million [11].

Complications of DM are secondary to macro and microvascular injuries [12]. The chronic-degenerative nature of DM characterizes it by inducing complications associated with macrovascular injuries, among which stand out: coronary heart disease, myocardial infarction and peripheral vascular disease. Complications associated with microvascular injuries include: end-stage renal disease, neuropathy and retinopathy [12,13].

DR is one of the main complications of DM that generates visual disability in adults of productive age; it is attributed that it affects the third part of patients with long-standing DM; however, it has been reported that the incidence of diabetic retinopathy in general, and proliferative diabetic retinopathy in particular, have decreased since 1990 to date [13,14]. This decrease is attributed to the control of risk factors, timely diagnosis of DM through screening programs, introduction of more efficient retinal treatments, as well as the reduction of tobacco consumption. However, it is estimated that by 2030, 191 million people will develop DR and 56.3 million with vision-threatening diabetic retinopathy (VTDR) [15].

Getting to lose sight of potentially preventable diseases, has social, economic and cultural implications that end up affecting the quality of life of the patient with DM; therefore represents an area of opportunity for the development of mathematical models that make it possible to understand the evolution of DM in its progression to DR [16], in addition to the design and operation of equipment and devices that help rehabilitate the visual capacity of patients with DR [17]. Advances in the understanding of the pathogenesis, pathophysiology and evolution of DR towards blindness have determined the intervention of the Medical Bioengineer at a preventive, diagnostic, therapeutic and rehabilitation level. At a preventive level, the devices used to determine the blood glucose control level [18], as well as the equipment used to monitor blood pressure and blood lipid levels, stand out. It also includes devices for screening and timely identifying retinal lesions [19]. At the diagnostic level, devices based on image processing stand out [20]. For the treatment of RD, photocoagulation and laser therapy, intraocular pharmacological intervention and ocular surgery stand out [21]. The rehabilitation of the visual system is aimed at the application of visual prostheses and implants that contribute to restoring visual function in the patient with blindness or decreased visual capacity [22,23]. The potential participation of the Medical Bioengineer in the VTDR, determines the need to understand the natural and social history of the health-disease process associated with DR, in order to recognize the chain of biological events that range from the persistence of risk factors to the installation of blindness in the patient with DM.

1.2. Natural history of diabetic retinopathy

The risk factors that increase the incidence of DR are: hyperglycemia, hypertension, dyslipidemia, duration of DM, pregnancy, puberty, and cataract surgery [15]. The persistence of these risk factors affects the progression of DR, going through the following stages: non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) [24]. According to the progression of the retinal lesions, each stage is disaggregated to define the degree of severity in the evolution of the disease (Table 1).

The risk factor of importance for the development and evolution of DR is the duration of DM, to which the glycemic control is associated. When DR is installed, glycemia acquires the greatest importance among risk factors, since it determines the homeostasis of the ocular internal environment and the retinal metabolism in DM. Diabetic retinopathy progresses sequentially when there is no adequate control, linking the alterations to the microvascular changes that are observed progressively in the retina; and will lead to a decrease in oxygen concentrations, causing the oxygen demand to increase. In this case, it is important to note that the retina has exceptionally high metabolic demands and the neural function depends on the constant availability of oxygen and nutrients [25,26].

Initially, DR is characterized by vascular anomalies in the retina, which evolve to the appearance of microaneurysms, intraretinal hemorrhages, venous dilatation and cotton-wool spots [27]. The next stage is characterized by alterations dependent on the increase in vascular permeability, which leads to thickening of the

retina associated with edema produced by extravasation of liquids and deposits of lipids that constitute hard exudates [24]. The blood vessels dilate, form loops and beading, increasing the extravasation that shows up as retinal hemorrhage and extensive exudates [28].

Table 1: Progression of retinal disease associated with DM

Progression of the disease	Characteristics
Retinopathy not apparent	There are no retinal abnormalities
Slight NPDR	Existence only of microaneurysms
Moderate NPDR	More than just microaneurysms but less than serious NPDR
Serious NPDR	More than 20 intraretinal hemorrhages in each of four quadrants.
	Definite venous beading in two or more quadrants
	Prominent Intraretinal microvascular abnormalities (IRMA) in one or more quadrants
	Prominent IRMA in one or more quadrants
PDR	Neovascularization
	Vitreous/preretinal hemorrhage
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	Mild diabetic macular edema: some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
	Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center
	Severe diabetic macular edema: retinal thickening or hard exudates involving the center of the macula

Source: American Academy of Ophthalmology Retina/Vitreous Panel [24].

The microvascular damage in advanced stages, induces the appearance of new vessels prone to generate vitreous hemorrhage, they are observed mainly in the optic disc, although they can develop in the iris and the angles of the anterior chamber producing neovascular glaucoma [29]. This stage of neovascularization is associated with ischemia, vasoconstriction and fibrosis in the retina. Retinal ischemia is attributed to the gradual closure of the retinal vessels, which induces alterations in the oxygen and nutrient perfusion required by the retina [24]. Fibrosis will lead to epiretinal membrane formation, vitreoretinal traction bands, traction or rhegmatogenous retinal detachment [30]. Finally, there is macular edema characterized by thickening of the retina and hard exudates adjacent to the center of the macula; They induce center-involving macular edema or non-center-involving macular edema [31].

The understanding of the evolution of DM, towards the loss of vision through the progression of the injuries produced in the retina, has led to the identification of indicators that allow the evaluation of the progression of DR. Among these is the digital analysis of images and biomarkers. The digital analysis of images allows to identify the caliber of the retinal vessels, the tortuosity of the vessels, the fractal dimension and the bifurcation angles; as well as the quantification of retinal vessel flow and level of oxygen concentration in blood vessels by means of non-invasive techniques that make it possible to obtain and process retinal images (wide-angle imaging systems, ultrawide field retinal imaging, wide-angle fluorescein angiography) [26].

The traditional concept of a biomarker is stated as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" [32]. However, it is also considered as "a biological molecule found in blood, or other bodily fluids, or tissue which represents a sign of a normal or abnormal process of a condition or disease" [33]. For the field of Medical Bioengineering, biomarkers linked to the disease are of interest, since they will show the progression of retinal lesions. These include genetic markers, microaneurysm replacement, subclinical macular edema, decreased percentage of retinal thickening [34].

1.3. The purpose of the study

Analyze epistemologically the emerging trends in the study of DR to characterize problematic fields and epistemic matrices that make it possible to integrate a horizon of understanding from the field of Medical Bioengineering.

II. Method

Even though research related to DR is relatively recent, it is based on logic of scientific research that has led to its rapid development, based on the dialectic of the construction and rational reconstruction of the thematic field of this disease. To explore this line of reflection, a methodological horizon was constructed, delimited by the following criteria: starting point, represented by the qualitative research that takes shape in the documentary analysis; the direction of the gaze that takes shape in the interpretive paradigm of hermeneutics in its application to the health-disease process [35]; horizon of the look that is operated through the lakatosian approach of the Methodology of Scientific Research Programs (MSRP) [36] specifying in the design of the study.

In this context, the elaborated methodological horizon contributes to establish the closeness between the scientific research of DR and epistemological reflection, so that the development of the study was divided into three stages [37]. The first delimited the bibliohemerographic content to construct the thematic field diachronically and synchronously from categories of analysis and identify the internal and external history of the DR. In the second, the components of the research program were determined: hard core, protective belt and heuristic (positive and negative). In the third, several problematic fields were identified.

2.1. First stage: construction of the thematic field

The thematic field represents the analytical-conceptual delimitation of the DR. It allows placing the subject in the process of opening reality through problematization mechanisms that involve the historical and articulated reconstruction of the real concrete (that is, the natural history of the DR), with the level of abstraction produced during the cut of the reality that leads to the development of research processes [38-40]. The thematic field, in this case, is the spatio-temporal cognitive dimension where reality and research processes are articulated, so that it is fed systematically by the question-answer dialectic of the problematization.

The construction of the thematic field in the study corresponds to the reconstruction of the internal historical development from the objective knowledge derived from the logic of the scientific discovery, to give way to the external history [36,41,42]; that is, to the social conditions in which the logical processes of DR research are developed.

At this stage, the following categories of analysis were determined: "diabetic retinopathy", "bioengineering", "medical bioengineering". These were used as Medical Subject Heading (MeSH) terms to retrieve articles from the databases of medical journals included in PubMed-NCBI and PMC-NCBI [43].In the period comprised between 2014-2018, a total of 27,311 records of publications related to DR were identified; Limiting the search with "bioengineering", 1,475 records were identified, and 1,019 records with "medical bioengineering". Relevant publications were retrieved through the secondary search system (Pearling) [44]. The review was conducted between January and October 2018. Only the scientific literature published in English was included.

2.2. Second stage: identification of elements of the MSRP

After having made the theoretical cut from the categories of analysis to characterize the thematic field of the DR, we proceeded to the identification of the elements of the MSRP: hard core, protective belt and DR heuristics; representing with it the scientific reconstruction that underlies in the logic of the investigation directed to clarify the pathogenic and physiopathological processes of the DR and to derive from there, the problematic field in the following stage. In this sense, the epistemological approach of the study focuses on the Lakatosian epistemological perspective exposed in the MSRP, which makes it possible to identify rival research programs as well as progressive and stagnant problems [41].

For Lakatos [36], the MSRP is the descriptive unit of the scientific advances in which sequentially scientific theories are integrated with space-time continuity, so that it is configured in the epistemological analysis unit.

The hard core is the structure that characterizes the MSRP and is integrated with general hypotheses, theories or universal statements that provide stability and support the entire MSRP. The hard core includes the scientific knowledge that has been conventionally accepted by the scientific community and is considered irrefutable [36,37,45].

The protective belt is composed of explicit auxiliary hypotheses, observation statements and assumptions that underlie the description of the initial conditions. It is located on the periphery of the hard core, having the function of protecting it; although it also interacts with him dynamically and thus update the MSRP [36,37,45].

The heuristic refers to the methodological rules that have allowed the development of research processes through the conceptual, methodological and empirical organization of the MSRP. The methods that must be avoided make up the negative heuristic and imply the impossibility of modifying the hard core, because the logical form of the *modus tollens* underlies it (the way that denies, denies); that is, the fundamental logical rule fully acceptable in a scientific discipline because of its high empirical content. The suggestions that make possible changes in the hard core constitute the positive heuristic, in a way that defines methods and problems to make sense of the protective belt from the construction of auxiliary hypotheses; reason why it anticipates the possibility that empirical evidences are identified that compete with other data obtained empirically [36,37,45].

2.3. Third stage: development of the problematic field

The problematic field is the articulation of a set of research problems that derive from the demarcation of the thematic field and is constructed from processes of clipping of reality sustained in problematization processes [38-40]. The problematization as a cognitive tool to develop the problematic field is generated by the

dialectic of question and answer. The questions arise from the questioning that is made to reality and the answer is inscribed in the hard core. When identifying unanswered questions, it is incorporated into the problematic field and will result in the outline of auxiliary hypotheses that will give meaning to the research processes. The problematic fields are contained in the thematic field and establish relationships with each other, configuring themselves in networks of problems [37].

III. Results

DR is a microvascular complication of DM, associated with long-standing hyperglycemia, and leads to the loss of the patient's visual capacity. It was described in 1855 by Eduard von Jaeger and the association with DM was confirmed in 1876 by Leber [46]. Arthur Ballantyne's studies carried out in 1945 showing the hair alterations related to the progression of DR, as well as studies aimed at testing endothelial cell dysfunction, and the use of fluorescein angiography, consolidated the paradigm of DR as a disease microvascular [47].

The elaboration of the ontological construct of the DR was a process that dates back more than 200 years (Table 2), but it is in 1851 when the first technological revolution is presented with the construction of the ophthalmoscope, making it possible to explore the fundus of the eye in patients with DM [48]. Eduard von Jaeger recognized the importance of exploring the inside of the eye and capture his observations in images, so he built an ophthalmoscope integrating the optical principles enunciated by Helmholtz and Ruete, and he also created a color atlas containing 21 images of the fundus [49].

However, the analysis of the pathogenic and pathophysiological mechanisms of DR from the approach of Medical Bioengineering requires the understanding of the visual function that man has. In this sense, the physiology of human vision is a process characterized by the transduction of light signals that come from the environment, to direct them to the central nervous system where images that allow man to visually explore his world of life will be integrated.

Table 2: Diachronic dimension in the construction of the DR concept

Year	Author	Event
1798	John Rollo	Describes concurrent ophthalmic lesions in patients with DM
1846	Appolinaire Bouchardat	Report the decrease in vision in patients with DM
1851	Herman von Helmholtz	Build the ophthalmoscope
1855	Eduard von Jaeger	Description of the DR using an ophthalmoscope
1869	Henry Noyes	Determined the correlation between diabetes and macular lesions
1876	Leber	Confirmation of the association of finding of the DR with DM
1921	Frederick Banting, Charles Best	Discovery of insulin
1945	Arthur James Ballantyne	Histopathological confirmation in specimens of hair changes in DR
1950	Gerhard Meyer-Schwickerath	Reports on the treatment of retinal disorders with photocoagulation
1963	Paul Wetzig	Introduces photocoagulation to the patient's clinical treatment
1968	Airlie House Symposium	The standardized DR classification system is elaborated
1979	Diabetic Retinopathy Study Research Group	The efficacy of pan-retinal photocoagulation for proliferative DR is confirmed
1985	Early Treatment of Diabetic Retinopathy Study	The efficacy of focal laser treatment for diabetic macular edema is confirmed
1993	Diabetes Control and Complications Trial	It is demonstrated that the intensive control of glycaemia decreases the risk of developing DR patients with type 1 DM
1998	United Kingdom Prospective Diabetes Study	It is demonstrated that the intensive control of glycaemia decreases the risk of developing DR patients with type 2 DM

Source: Wolfensberg and Hamilton [46], Shah and Gardner [47], Matuszewski et al [48], Kalantzis et al [49].

Human vision is composed of three functional components: optical, receptor and central neurophysiological [50].

The optical function falls on the anatomical structure of the eye, which behaves like a camera. For this reason, it is important to incorporate basic principles of optics such as: the refraction of light and the physics of lenses; which allows analyze the refractive index, as well as the focal distance, the depth of focus and calculate the dioptric power of a lens [51]. In this process, the cornea, the lens, the iris and the pupil participate, muscular structures that regulate the accommodation (suspensory ligaments, ciliary muscle) as well as the eye movements (intrinsic and extrinsic muscles of the eye), and nervous (parasympathetic nerve signals from of the nucleus of the third cranial nerve located in the brainstem) [52]. In this context, the eye becomes a sensorimotor unit that enables the binocular vision and spatial orientation that characterizes the human being.

Epistemologically two theories have been constructed to explain binocular vision and spatial orientation: empiricist theory and nativist theory [53]. The empiricist theory, circumscribed to the Galilean scientific tradition [54], holds that binocular vision and spatial orientation depend on ontogenetic development; that is to say, they are functions that are acquired by trial and error through the experience in which the other senses participate, especially the kinesthetic one [53]. The nativistic perspective considers that binocular vision

and spatial orientation are acquired phylogenetically; that is, both functions are innate and are determined by the anatomical and physiological organization of the visual system [53], which is why it is located in the scientific tradition of an Aristotelian nature [55].

The anatomical, geometric and physiological structure of the retina has its own mystery, for it has fascinated both Eduard von Jaeger [56] and Santiago Ramón y Cajal [57]. The retina is the fundamental structure that performs the receptor function of the visual system. It is a thin structure, integrated by multiple layers between which the neuronal bodies are located; reason why it is considered that it has two components: the neuroretina and the retinal pigment epithelium [58]. Neuroretin is basically integrated into three layers of nerve cells and two plexiform layers [59]; however, a more detailed description of the human retina shows that its architecture integrates several laminar regions that, in addition to differing structurally, fulfill specific functions (Table 3) [60,61].

In this context, the retina is traditionally presented as a tissue in which photoreceptor cells are concentrated that have the function of transducing and driving the light stimulus from the environment, into the visual cortex and, consequently, constructing the image in the consciousness of the human being. However, scientific studies using technological advances in microscopy, imaging and cellular marking, show the retina as a neuronal circuit that transcends the conception of a simple space-time luminous pre-filter, and is oriented towards the conception of work networks that selectively and specifically process the luminous information [62].

Table 3: Layers of the human retina

Retinal layer	Characteristics
Internal limiting membrane	Structure of basement membrane formed by the footpads of Müller cells.
Layer of nerve fibers	Formed by ganglion cell axons, it transports the visual signal to the visual cortex in the brain through the optic nerve.
Ganglion cell layer	It contains the bodies of amacrine and ganglion cells cells.
Inner plexiform layer	It contains synapses of the neural networks that are established by connecting the second order neurons (bipolar and amracrine cells) with the dendrites of the ganglion cells.
Inner nuclear layer	It contains the cell bodies of the bipolar, horizontal and amacrine cells.
Outer plexiform layer	Formed by axons of photoreceptor cells and their synapses with bipolar cells. It contains synapses of neural networks that are established between the photoreceptor cells that connect with the second order neurons (bipolar and horizontal cells). In general, bipolar "on" cells end on the inner side of the inner plexiform layer and the "off" bipolar cells end on the outer side of the inner plexiform layer.
Outer nuclear layer	It contains nuclei of photoreceptor cells (cones and rods).
External limiting membrane	It is not a true membrane. It is formed by structures of union of cellular bodies of cones, rods and Müller cells. Separates the internal and external segments of the nuclei of the photoreceptors.
Rod and cone layer	Composed by the external and internal segments of the photoreceptors (cones and rods); it houses the extensions of these receptors towards the pigmentary layer. The outer segment contains stacks of membrane discs, which enclose visual pigment molecules and are constantly renewed.
Retinal pigment epithelium	It is the outermost layer of the retina. It is located below the photoreceptors; that is, between the neuroretina and the choroid. It is a monolayer of cuboidal cells containing melanosomes from which the cells obtain their pigmented color. The extracellular space between the photoreceptors and the RPE contains a fundamental glycosaminoglycan substance (inter-photoreceptor matrix).
Bruch membrane	The basal membrane of the retinal pigment epithelium comprises the cuticular portion (inner layer) of the Bruch membrane. The rest of Bruch's membrane is composed of an internal collagen zone, a central zone of elastin, an outer collagenous zone and the basal membrane of the choriocapillary layer. The Bruch membrane separates the retina and the RPE from the underlying choroid. Defects within this membrane promote the growth of choroidal vessels in the subretinal space in choroidal neovascularization.

Source: Gupta et al [58], Wässle and Boycott [59], Hoon et al [60], Masland [61].

The retina occupies approximately 66% of the inner back of the eyeball; it has as limit previous to the *ora serrata*. Topographically the retina is divided into the following regions: macula, fovea, peripheral retina, and the optic nerve region. The macula has a diameter of 5-6 mm and a cone density of 4,000 to 5,000 / mm^2. In the center of the macula is the fovea, which has a diameter of 1.5 mm, has a cone density of 15,000 / mm^2 [63]; in addition, the fovea cones can establish synapses with 5 ganglion cells, while in the rest of the retina, a ganglion cell can be connected with 130 different photoreceptors. These characteristics of the fovea make it possible to participate in visual acuity and color vision [58,64]. In contrast, it highlights that the peripheral retina contains around 5,000 cones / mm^2 and up to 150,000 rods / mm^2 [65].

The light signals from the environment are finally processed in electrical signals, which after being processed in the retina are transmitted to the brain, reaching the primary visual cortex, to trigger the processes of visual perception and unconscious behavior such as: eye movements, pupillary reflexes, and circadian rhythms. Returning to the interest and objective of the study, we explore below the horizon of meaning.

3.1. Horizon of meaning

Understanding the DR is shown as a multidisciplinary task of high complexity, so that each discipline is transiting its own path of scientific inquiry. In this sense, biomedical researchers in the area of health sciences are directed to characterize the biological, cellular and molecular mechanisms that participate in the normal and pathological functions of the retina; Medical Bioengineers, like the other disciplines of medical engineering, are directed to the development of devices of clinical and scientific utility; while social scientists are oriented to the sociological and anthropological analysis of DR and the appropriation of technology in the daily life of the patient. Finally, the path of the medical humanities, undoubtedly the least traveled of all, ventures into the understanding of a personalized, holistic and comprehensive medicine where the DR is incorporated into the patient's worldview, impacting the visual arts, the history of the concept, and the conceptual structure of the scientific and conceptual advances of specific problematic fields that affect the patient's daily life when interacting with their world of life; or, problems of a philosophical nature such as "the neural correlation of consciousness" [66].

In this context, and following the path of teleological reflection that prevails in Medical Bioengineering, the different paradigms that are developed are based on the unity of the visual system, already enunciated by Ramón y Cajal in 1933 [67], which implies the recognition of the integration between structure and function of the cells that participate in human vision at the retinal level. Because of its histological and functional nature, the retina is shown, first, as a window into the world of life, and then, as the threshold to look into the interior of the human brain. Thus, the eye is shown, from the Galilean tradition, as an optical instrument that is equated with a photographic camera, and from the teleological tradition, as a computational system sustained in the network of circuits that express the connectivity of the retinal cells.

The retinal mystery that is gradually elucidating is determined by the complexity of the human vision; which is not limited to the perception of the existing objects in the patient's life and has been reduced to binocular vision and orientation spatial, but in understanding the ability of the retina to participate in the analysis of the movement of objects, as well as in the identification of recognition patterns of objects. These functions are performed on the retina by eight cell lines (table 4) [58,68], which have been described from the histological, biochemical, physiological and electrophysiological point of view. But it is through the integration of physics, mathematics, biology, and computer science, the point of convergence offered by a direction to the development of Medical Bioengineering in the DR field, favoring the incorporation of areas of opportunity to the evaluate the DR paradigm as a microvascular disease, among which stand out: computer science, robotic vision, and artificial intelligence.

Table 4: Cell types of the human retina

Cell Types	Characteristics
Cones	Photoreceptor cell that contains iodopsima, includes three types: S-cones, represent 16% and are stimulated in a wavelength range of 420 nm (blue); M-cones represent 10% stimulating at a wavelength of 532 nm (green); and L-cones that represent 74% and are stimulated at a wavelength of 558 nm (red). They participate in the color vision.
Rods	Photoreceptor cell containing rhodopsin; they participate in night vision and peripheral vision.
Retinal pigment epithelial cell	They facilitate the diffusion of nutrients from the choroid to the external neuroretina retina, as well as the elimination of the photoreceptor segments. Each cell serves up to 45 photoreceptors.
Horizontal cells	Two cell types have been identified. They are, mainly, GABAergic neurons (γ-aminobutyric acid), which connect to cones or rods and establish synapses with bipolar cells, where the "on" and "off" responses are generated to regulate signal transduction.
Bipolar cell	Ten cell types have been identified. They are glutamatergic or glycinergic neurons, which connect the photoreceptor cells ultimately with the dendrites of the ganglion cells in the outer plexiform layer.
Amacrine cell	24 cell types have been identified. They receive excitatory glutamatergic input stimuli from bipolar cells and input stimuli primarily inhibitory to other amacrine cells mediated by GABAC receptors. Amacrine cells can support the synapses with bipolar cells, amacrine cells and / or ganglion cells.
Ganglion cell	Includes 10 types. They receive information by stimuli from bipolar and amacrine cells. They participate in the receptive field of the retina; thus, the receptor field is the area of the retina whose stimulation can modulate the frequency of discharge of the ganglion cell.
Müller cells	They act as specialized glial cells to form retinal scaffolds, support the internal segments of the photoreceptors and create the acellular fibrous internal limiting membrane.

Source: Gupta et al [58], Masland [68].

In the first level of intervention of the Medical Bioengineering, at the level of the optical function of human vision, devices are developed to determine the optical properties of the eye (table 5), mainly to evaluate the refractive index, the separation of surfaces, the relative central state and the quality of the beam transmitted, as well as the focal length [69]. Although image processing analysis involves both linear and non-linear processes, Fournier's theory [70] is useful for determining the image of the retina with the point scatter function [71] and the optical transfer function.

In the second level of intervention of the Medical Bioengineering, at the level of the receptor function attributed mainly to the retina, the analysis of the luminous stimulation of the photoreceptor cells is carried out: cones and rods; which results in the processing of electrical signals and images. Yellott et. al. [73] identify three kinds of explanations of the perceptual phenomenon, which are of interest for the development of devices that contribute to the restitution of the visual function of the human being. The perceptual processes included in the first explanation class are "phenomena whose properties can presently be explained in terms of accepted physical principles together with well-established anatomical and physiological properties of the visual apparatus" [73], in addition to representing the phenomena associated with the loss of perceptual information, as is the case of color vision and the function of spatial modulation transfer function. For the case of the DR, it corresponds to the processes described in the hard core section of this communication.

The explanations of class 2, includes the "visual phenomena for which one can envision plausible physiological models, but for which the specific anatomical or physiological mechanisms remain uncertain" [73]. Preceding the paradigm of the loss of perceptual information, it addresses the analysis of light sensitivity phenomena, such as adaptation to light and darkness, linking psychophysical evidence with electrophysiological recordings of photoreceptors, and heterochromatic brightness. In the case of DR, it corresponds to the processes described in the section of the protective belt of this communication. The perceptual phenomena of class 3 enunciated by Yellott et al. are "visual phenomena for which we have no clear conception of even the outlines of a physiological explanation" [73]; as is the case of subjective phenomena such as visual images, visual experiences in dreams and hallucinations.

Table 5: Optical properties of the eye

Structure	Optical Property	Fact
Eye	Optical power	60 diopters
	Focal length	16.7 mm in air
Cornea	Optical power	40 diopters
	Transmission	It is highly transparent with a transmission greater than 95% in the spectral range of 400-900 nm.
	Refractive index	$n \approx 1.3765 \pm 0.0005$
Pupil	Size	Between 1.5 mm and 8 mm
Aqueous humor	Refractive index	$n \approx 1.3335$
Crystalline	Refractive index	$n \approx 1.40\text{-}1.42$
	Dimensions	Approximately 4 mm thick and 10 mm in diameter.
	Optical power in relaxation	20 diopters
	Optical power in maximum accommodation	33 diopters
Vitreous humor	Refractive index	$n \approx 1.335$

Source: Gross [69].

In this context, electrical signal processing highlights the electroretinographic recording of the retinal electrical signal produced by the excitation of the photopigments that lead to a visual response [74]. In addition, the possibilities of technological application are broadened, as it is focused on obtaining retinal images, so the image is processed to reduce noise, filter the edges, separate the colors and compress the obtained image [75]. Finally, the stimulation of the cerebral cortex makes it possible to reconstruct the image, interpret it, subjectively assign it a specific connotation, so that in the central neurophysiological function, the electrophysiological, image and functional techniques acquire importance for the analysis of movement [76], recognition of patterns [77], objects and other processes occur in the brain [78]. The contributions of Medical Bioengineering to human perceptual phenomena have contributed to explore the relationship between image, brain stimulation and human affectivity [79], and even the neurobiology and neurophysiology of aesthetic judgment [80].

3.2. Hard core: logic of the pathophysiological investigation of DR

The scientific development oriented to the investigation of the physiopathological mechanisms of DR has been based on mechanistic models aimed at supporting the theory of vascular damage [27]. Subsequently, scientific evidence showed decreased retinal ganglion cells [81,82], loss of amacrine cells [83] and the participation of photoreceptors in microvascular damage [84], which substantiated the theory of neuronal damage. The neurodegenerative theory associated with the inflammatory pathogenesis of RD is currently under development [85].

By developing these ways of explanation, with the intention of understanding the evolution of molecular and cellular damage caused by hyperglycemia in the retina of the patient with DM, they recovered, rehabilitated, reconstructed and incorporated knowledge from other scientific disciplines of the natural sciences and the engineering, which have allowed the design of bioelectronic devices used in the diagnosis [86], treatment [87] and rehabilitation [88] of DR, to limit or recover the reduction of vision or blindness.

In this context, the Lakatosian model of the MSRP places the firm nucleus as the fundamental epistemological structure in which the knowledge scientifically consolidated and accepted by the scientific community are linked; so that they are considered irrefutable and provide stability to the disciplinary fields of scientific research [36,45]. Thus, the hard core in the development of the thematic field of RD of interest to Medical Bioengineering is limited to the mechanistic and teleological expressions of the theory of vascular and neuronal damage, as well as the application of biophysical theories of the membrane and the electrophysiology.

The hard core is consolidated from the theory of vascular damage that is based on the thickening of the basement membrane and the hypertrophy of the extravascular matrix, characteristics of the microangiopathy produced by DM. This theory explores the evolution of vascular alterations at the biochemical and electrophysiological level to clarify alterations in the structure of the retinal vessels and hemodynamic functionality [89]. In the process of understanding, cable theory is applied to explain the transmission of the nerve impulse in the visual pathway [90]; Ohm's law to understand cellular structures from electrical circuits; and it uses the fast Fourier transform for the analysis of the information obtained experimentally or clinically.

From studies in which these knowledges are combined, specifically the electroretinogram (ERG), the visual evoked potentials (VEPs) and ocilatory potentials (OPs); they make it possible to understand that the logic that underlies the pathogenesis of DR considers, at first, the progressive changes of homeostatic mechanisms that alter the functionality of the retinal blood vessels [26,28,91]. Studies with multifocal ERG (mfERG) show evidence of retinal functional alterations before microangiopathic alterations are observed [92]. That is, the microenvironmental conditions produced by the constant hyperglycemia in the retina increase the oxidative glycation by increasing the final products of advanced glycation (AGES). In addition, hyperglycemia produces oxidative stress that stimulates the production of cytosines, and the expression of vasoactive mediators such as endothelin, thus amplifying the damage to the retinal vasculature.

Subsequently, structural alterations occur in the smooth muscle cells of arterioles and capillary pericytes. Pericytes are cells that participate in angiogenesis and in the permeability of vessels, but in patients with DM it has been reported to decrease their number and increase the apoptosis of these cells, promoting alterations in the control of endothelial proliferation as well as in the vascular permeability [93].The decrease in pericytes is associated with the consequent decrease in the transforming growth factor beta (TGF-β), which indirectly induces the decrease in the inhibition of endothelial proliferation. In this sense, the functional homeostasis of the vascular structures is first altered, reflecting in the increase of glucose flow that goes to the pathway of polyols and hexosamine, activation of protein kinase C, and increase in the formation of end-product products. the advanced glycation of glucose [94]. As a secondary event, the hemodynamic characteristics of the retinal vessels are modified, among which we find the blood flow (volume and velocity), oxygen perfusion and elasticity of the blood vessels. To assess the blood flow of the retinal vessels, it is possible to apply the pressure attenuation index proposed by Quigley and Cohen [95]. This index relates the expression of Ohm's law in terms of the differential of flow and resistance along a tube, with Poiseuille's law to determine the resistance of the flow in a tube, and Murray's law that evaluates the flow in blood vessels; expressed in the following terms: PAI=L / D; where L is the length of the vessel and D the diameter of the vessel. When persisting the internal environment with high concentrations of glucose, the structural damage associated with the decrease of pericytes, thickening of the basement membrane, neovascularization and alteration of the blood-retinal barrier, is made manifest through the diameter, tortuosity and thickness of the retinal blood vessels [27].

The theory of vascular damage, centered on the pathophysiological process that underlies alterations in the hemodynamic characteristics of retinal capillaries, is associated with the regulation of capillary flow in such a way that they contribute to the exchange of nutrients, oxygen and metabolites between the neuropil and the circulation; that is, they contribute to the regulation of the homeostasis of the internal environment of the retina, making it easier to compensate for regional changes in the oxygenation of the retina and ocular perfusion pressure. The retina presents regional differences in the thickness of the layers that make it up so that a demand for regionally differentiated oxygen consumption in the retina will be observed [96]. In addition, the more than 60 types of cells that make up the retina present oxygen consumption rates associated with their functions. Photoreceptors (cones and rods) have the highest oxygen demand, especially during depolarization that occurs in the absence of light, because maintaining the "dark current" requires the activity of the Na^+/K^+ ATPase. The importance of the homeostatic balance of oxygen concentration in the retina lies in the hypoxia that underlies the early stages of the pathogenesis of DR. To evaluate retinal oximetry, several methods have been used, among which the retinal function image (RFI) [97], the multispectral imaging method [98], optical coherence tomography (OCT) [99], as well as images using transcranial fundic spectroscopy, described by Weber and Mertz [100], have been used a method that uses near infrared light for deep penetration.

The result of visual deterioration; ranging from the weakness of the vascular wall and changes in pressure that give rise to microaneurysms, allows the filtration of fluid that causes separation of the photoreceptors, formation of new blood vessels susceptible to hemorrhage, obstruction and closing of capillaries, reaching retinal detachment by traction.

To explore, identify and analyze the retinal processes linked to vascular theory and the theory of neuronal damage, various methods of scientific and clinical interest have been used to obtain retinal optical images such as capillary perfusion maps and blood flow velocity [101]. The obtaining, processing and analysis of retinal images has become a scientific field of self-development, transiting through significant advances in the whole process of retinal imaging, which includes angiography (with fluorescein and with green indocyanine), the laser ophthalmoscopic scanner, and OCT [91]. More recently, angiography with OCT, photoacoustic microscopy (PAM), adaptive optics (AO), fundic autofluorescence (FAF), and molecular imaging (MI) have been introduced to research and clinical practice. All these methodologies to explore the confines of the retina converge without doubt in the development of artificial intelligence [102].

Consequently, the hard core of the DR also includes the participation of computer science, which enables the development of mathematical models that concentrate clinical findings, as well as experimental data from studies conducted in laboratory animals; with the purpose of theoretically analyzing the structure/function relationship of the retina; or, the vascular architecture through the multifractal geometry [103]; but also to anticipate the progression of retinal diseases such as DR [104].

3.3. Protective belt: Neurovascular unit in DR

DM is currently a chronic inflammatory state associated with metabolic dysfunction that leads to the increase of vascular inflammatory elements [105], closely linked as a process of "metaflammation", in which converges chronic and low-grade inflammation with excess energy [106]. In this context, the retinal damage described as an event that underlies the installation and progression of DR, is associated with the presence of pro-inflammatory molecules that accompany the pathophysiology of DR, so that the neurodegenerative theory is consolidated in the horizon of understanding the inflammatory pathogenesis of DR [85].

For the epistemological analysis of the scientific discourse that prevails in the study of DM, placing DR in the scenario of conceptualizing DM as an immunological disease, tests the conception of the protective belt of the MSRP. Lakatos indicates that the protective belt is integrated with explicit auxiliary hypotheses, observational statements obtained empirically and theoretical assumptions that underlie the description of the initial conditions that determine the appearance of the phenomena [36,45]. In this sense, the conceptual development of the pathogenesis of DR has incorporated the inflammatory theory as a mechanism linked to the neurodegenerative process faced by retinal cells during DM.

This implies that scientific advances are grouped in the protective belt, located in the periphery of the hard core, and will remain in that place until knowledge is accepted as a component of the hard core, of knowledge that will be considered intangible and that will maintain it dynamically updated; so that the protective belt protects the hard core of those discoveries that later come to be refuted [45]. This is the case of the development of the concept of DM as a process of "metaflammation", which has led to review the metabolic, hormonal, epigenetic characteristics and oxidative homeostasis that underlie DM from the scope of immune homeostatic processes [107]. Immunological evidences associated with the pathogenesis of DR lead to new approaches; For example, what are the direct effects of hyperglycemia on the retina of the patient with DM? Based on the evidence of the correlation between hyperglycemia and the homeostasis of oxidative pathways, the hypothesis of the participation of oxidative stress in the development and progression of DR is proposed [108].

The hyperglycemia in the retinal microenvironment promotes the increase of the polyol pathway, the formation of end products of advanced glycation (AGEs), activation of protein kinase C (PKC) and the hexosamine pathway. These events increase the formation of free radicals of O2 and oxidative stress, inducing the rupture of hematorretinal barrier (BRB), increasing capillary perfusion and extracellular fluid, vascular occlusion and ischemia [109]. Furthermore, by maintaining hyperglycemia regionally, the increase of pro-inflammatory molecules (interleukin 1β, tumor necrosis factor alpha, interleukin 6, interleukin 8) is promoted, which will lead to the disruption of BRB, which is shown as the target organ of the inflammatory pathogenesis of DR and have been associated with the increase of glycosylated hemoglobin.

BRB regulates the retinal microenvironment and is formed by tight junctions that establish the epithelial cells located between RPE and the endothelial cells of the retinal capillaries [110]. Currently, two components are recognized: the external and the internal. The internal BRB is involved in the pathogenesis of DR; because the regulation of the microenvironment is determined by the function of restricting the non-specific transport of molecules between the neuroretina and the blood; so that a strict control of fluids and solutes that prevent the entry of toxic molecules and plasma components to the retina is maintained. *In vitro* studies have identified that the hyperglycemic microenvironment alters the functions of the proteins involved in the formation of tight junctions of the BRB, which include three types of transmembrane proteins: occludin, claudin and junctional adhesion molecules (JAMs) [110].

The dysfunction of the BRB in the DR involves the junctions between the endothelial cells of the retinal vessels that lie between the inner nuclear and outer plexiform layers of the retina, which constitutes the

internal BRB; it is presented as a consequence of the constriction of the retinal vessels that induce the decrease of retinal perfusion, as well as blood flow, which triggers the appearance of ischemia, especially in those regions with the highest oxygen demand. The rupture of the barrier generates leukocyte migration as well as the accumulation of plasma proteins in the retinal tissue, increasing the oncotic pressure and, consequently, interstitial edema, thickening of the basement membrane of the internal nuclear layer and separation of the photoreceptors.

Chronic hyperglycemia, as well as the accumulation of free radicals of O_2 and AGEs, induces the death of pericytes. The pericytes surround the endothelial cells and exert the contractile function maintaining the vascular tone and the integrity of the vascular wall. By decreasing the number of pericytes due to apoptosis, the capillary sacculation is developed, which results in the appearance of microaneurysms and retinal hemorrhages.

The immunological alterations induced by the hyperglycemic microenvironment in the retina, also affects the neurovascular junction, in which the neurons, the glia, the retinal vessels and the central nervous system intervene. The dysfunction of this unit affects the signaling and synaptic transmission of the photoreceptor cells of the retina. In the case of neuroretina, the appropriate ionic environment for signaling and neural transmission involves the capillaries near the ganglion cell layer and the inner nuclear layer, as well as the astrocytes and amacrine cells. The electrochemical impulses induced by photostimulation generated in the external retina are reduced due to the decrease in the electrical activity of the photoreceptors and of the Müller cells, furthermore, under conditions of hyperglycemia, the Müller cells produce nitric oxide, cytokines and prostaglandins (PGE2, PGD2, PGF2 ALPHA, PGI2 and thromboxane A2) [109].

Faced with this type of processes that develop in subclinical stages of DR, questions arise related to the electrochemical and electrophysiological properties of the retina, but also to the processing of signals and impulses produced by the photonic stimulation of retinal cells. For example, in the different clinical stages of DR, how can the brain expect to decipher the ganglion cell peaks and reconstruct the image in the retina? [62] In this sense, it is important to state three general principles outlined by Masland in 2012 [111], which regulate the understanding of the neural networks that underlie the retina and participate in the visual perception of objects. These principles are:

- "The signal generated by any individual cone is decomposed into ~12 different components, each of which is transmitted separately to the inner retina by a structurally and molecularly distinct type of bipolar cell" [111].
- "The outputs of these bipolar cell channels are sampled by different sets of retinal ganglion cells" [111].
- "The partially selective responses mediated by bipolar cells are refined by amacrine cells—a few per ganglion cell type—to create arrays of precisely specific ganglion cell subtypes" [111].

In this order of ideas, DR is shown as a peripheral sensory neuropathy.

3.4. Heuristic: exploring ways to understand DR.

The access to the retina through the ophthalmoscope showed the way to go to elucidate the retinal alterations that develop in patients with DM. Recognizing the subjective clinical manifestations enunciated by patients, the elucidation of the pathogenic and pathophysiological processes have used different methodological rules to conduct the research processes and organize them conceptually, methodologically and empirically [45,112]; that is to say, in the scientific investigation of the DR, a heuristic underlies, which in Lakatosian terms refers to the methods and rules that lead to discovery and invention; so it identifies two types of heuristics: the negative heuristic and the positive heuristic [36].

From the perspective of Lakatos, the negative heuristic is directed to the analysis of research methods and rules that should be avoided as the results obtained through these methods do not have the possibility of modifying the hard core [36]. For example, in the decade of the 50's of the last century, hypophysectomy was performed on patients with severe retinopathy, obtaining improvement in only 30% of cases [49]. The scientific argument was the observation that in a patient with postpartum pituitary necrosis the proliferative DR presented improvement [114]. Another example that shows the value of the negative heuristic from the lakatosian perspective is presented in the use of the angiographic OCT that does not allow to see filtrations in the retina, so it is not recommended for the study of BRB [110].

The positive heuristic, in the lakatosian perspective, helps to define the methods that will lead to the study of problems associated with the application of engineering to the biological phenomena of diabetic retinopathy, so that they guide the construction of auxiliary hypotheses that are tested in the protective belt [36,41]. The methodological approaches can be grouped into four categories: biological, imaging, electrophysiological and computer.

From the biological approach, different models that are being developed in the field of DR study stand out. These can be grouped into: animal models, tissue models and cellular models. Animal models in the study of DR have contributed significantly to the knowledge of the pathogenesis, pathophysiology, clinical evolution, diagnosis and treatment of this disease [115,116]. The species used include mice, rats, rabbits, cats, pigs,

zebrafish and non-human primates. Currently rodents, mice and rats are widely used. These species have been classified as induced models, spontaneous models, and genetically engineered models [117]. To induce DR models the following methods are used: surgical (pancreotomy), chemical (administration of streptozotocin or alloxan), dietary (diet rich in galactose), physical (eye injury with laser ray) and hypoxic damage. Currently, genetic models are available in mice, rats and zebra fish.

The lesions that occur in the diabetic retina have been described for many decades using descriptive and experimental approaches based on clinical studies in patients, post-mortem human material, animal models and various *in vitro* systems. With the introduction of neurodegenerative theory linked to inflammatory processes in the pathogenesis of DR, the use of dissociated or organotopic retinal cell cultures has been promoted [118]. In addition, the analysis of the participation of microRNAs in the pathophysiology of DR has been made possible [119].

The imaging approach groups the appropriate techniques for obtaining, processing and analyzing images of the retina and includes the following [91,120]: fundic photography (FP), fundic fluorescein angiography (FFA) and optical coherence tomography (OCT).

In the electrophysiological approach, retinal evaluation techniques are grouped through their electrophysiological properties and include the following [91,120,121]: electroretinography (ERG), pattern ERG (PERG), multi-focal ERG (mfERG), oscillatory potentials (OPs) and visually evoked potentials.

The multiplicity of biological models; as well as the development of technology applicable to the clinical, and experimental study of DR, reflect that more questions than answers are being produced. Some questions face the limitations of transferring the information obtained in the models, to the clinical evolution of the patient with DR, either for diagnosis, prognosis or treatment. For this reason, computer models have been developed, understood as a "is a set of mathematical equations, with algorithms for combining these equations with computer software" [122]. The appearance of computer models during the last decades, led the American Diabetes Association to publish a set of guidelines to give certainty to the use of these models. Among the defined criteria are [122]: transparency, internal and external validation, measurement of the uncertainty of the parameters used (ignorance, known variability, statistical variability, Monte-Carlo variability, and uncertainty around the design of the model), and specification of special requirements.

In accordance with these guidelines, multiple models have been developed; for example, to evaluate the effect of peripheral photocoagulation on the development of DR [123]; or, following the teleological logic of the visual system, an algorithm is constructed that considers the sensitivity of the retina for the diagnosis of DR [124]. The advances continue to be directed towards providing computer models that simplify the analysis of images to assess the severity and evolution of RD through the use of learning of deep visual characteristics (DVF) [125].

In this regard, we highlight the models that use fuzzy regression models to predict the installation of DR in patients with DM. The development of these models is a function of the interests and objectives of the researchers, for example, by means of a fuzzy type 2 regression model, the progression of DR is associated with the age of diagnosis of DM, the concentration of glycosylated hemoglobin (HbA1c), fasting glycemia, and blood pressure [126].It is also used to make clinical decisions during DR screening [127].

3.5. Problem fields: understanding horizons in DR

It has gone through a conceptual network of epistemic unit making it possible to demarcate the DR as a thematic field of interest for Medical Bioengineering. Dominated by medical discourse, the DR appropriates a language phenomenon that gives it a charter of ontological naturalization as a form of existence. In this sense, a discursive space is generated, in which we can situate the natural history of DR. In the context developed by Maciag [128,129], DR discourse is constituted as an area of symbolic representation of reality that has the potential to be expressed mathematically, so that it emerges into the world of life as a space where the scientific discourse of the DR defines the trajectory of knowledge and organizes it socially according to human experience and subjectivity.

By cutting reality from this perspective, the theoretical and practical need to venture into the DR field is exposed through transdisciplinary approaches that enable the flow of knowledge between different scientific worldviews of reality; that is, the exchange of knowledge between the world of facts, the Heideggerian factual world or the world of Husserl's life and the cognitive system that emerges from the knowledge of specific processes and phenomena. Thus, from the discourse space emerges a system of knowledge of the world that is subordinated to the use of knowledge [129].

In this context, the analysis of the components of the MSRP has contributed initially to characterize DR as a complex research program, developed from the scientific tradition of a teleological nature, and exposes the need for deepen the pathogenic and pathophysiological mechanisms that underlie its spatio-temporal evolution of the natural history of the disease. This tendency induces to cut the reality through problematic fields of the DR that group research problems demarcated by the tools that provides the syncretism of the heuristics of the

natural sciences and the medical sciences. With this intention, it is possible to follow three paths to cut the DR's thematic field: the transdisciplinary meta-narrative, the structure of the natural history of the disease, and the levels of prevention. When carrying out this task, it must be borne in mind that the flow of knowledge between problem areas, whatever the cut of reality, are reaching levels of specialization that require the disaggregation and characterization of very specific problematic networks in which they require specific disciplinary concepts, particular methodological tools and appropriate terminology to establish scientific dialogue within fields.

The transdiciplinary meta-narrative that is permeating the conception of the scientific and professional field of Medical Bioengineering [130] generates networks of problems that can be grouped into three thematic fields: biomedical, clinical and the transdisciplinary approach of Medical Bioengineering (TAMBE). Table 6 presents some problematic axes circumscribed to each thematic field. It highlights the emergence of technological advances at the level of robotics, nanotechnology, biomarkers, tissue engineering and computer models that are currently being applied to DR research.

Table 6: Problematic axes circumscribed to the transdisciplinary meta-narrative

Thematic Field	Problematic axes
Biomedical	Development of technological tools for obtaining, processing and analyzing images, as well as electrophysiological signals, which contribute to the development of biomedical research oriented to the pathogenesis and pathophysiology of DR. Among these, tissue engineering and nanotechnology stand out.
Clinical	Development of processes, products, services and clinical application devices that contribute to the prevention, diagnosis, treatment and rehabilitation of DR. It highlights the use of computer models both preventive and prognostic, as well as the identification of biomarkers of clinical utility and the development of biomaterials.
TAMBE	Development of innovations oriented to the design of visual prostheses, retinal implants, robotic assistance (humanoid robots).

During the installation and evolution of the DR, does the damage produced in both eyes of the patient have the same degree of progress? Does the effort to focus the image, produces alterations in the optical system of the eye? Even when the mechanism of visual self-compensation is recognized, the previous questions are some of the problems that open the possibility of viewing the visual system as an optical system [131], so that technological tools aim to improve the level of resolution, as is the case of OCT of the anterior segment of the eye [132], which is why dual modality systems are being used to obtain anatomical and physiological information of biomedical and clinical interest, such as the case of obtaining of photoacoustic and ultrasonographic images concurrently [133]. In the same sense, the clinical interest is being directed to the evaluation of lesions at the level of the peripheral retina [134].

The development of methodological as well as technological applications that are contributing to the development of the immuno-engineering area [135] is shown as an interesting alternative to contribute to the consolidation of the immunologically induced degenerative theory; this also establishes the investigation of the pathogenesis of retinal diseases from the epigenetic paradigm, exploring ocular micro-environmental relationships between the microbiota and intraocular inflammation [136], which leads us to ask: the alterations in the microbiota described in DM contribute to the installation of the DR?

On the other hand, it is possible to define problematic fields by means of the cut of the reality, process oriented by networks of problems in relation to the periods of the natural history of the DR: prepatogenic, pathogenic and pos-pathogenic. Table 7 presents some problematic axes associated with the components of the natural history of DR. In this area, the development of applications for cell phones of ophthalmological interest stands out, which is revolutionizing the screening strategies to carry out the early diagnosis of retinal alterations in patients with DM, developing widely in this sense, based on smartphone photographs [137,138].

Table 7: Problematic axes circumscribed to the periods of the natural history of the DR

Periods	Stages	Problematic Axes
Prepatogenic	Agent	Development of computer models that simulate the response of retinal cells in hyperglycemic environments as well as the use of virtual biomodels.
	Host	
	Environment	
Pathogenic	Subclinical	Development of technological tools for obtaining, processing and analyzing images and electrophysiological signals that contribute to the development of biomedical research oriented to the pathogenesis and pathophysiology of DR. Among these, tissue engineering, nanotechnology and devices for screening in patients with DM stand out.
	Clinical	Development of innovations oriented to the design of surgical robots, artificial organs and 4D printing, synthetic materials that interact with the biological structures of the retina.
Pos-pathogenic	Healing	Development of innovations oriented to the design of visual prosthesis, retinal implants, robotic assistance (humanoid robots), artificial intelligence and augmented reality.
	Chronicity	
	Disability	

It is also possible to define problematic fields by trimming the reality oriented by the problem networks in relation to the levels of prevention of the disease: primary, secondary and tertiary (table 8). We must now

consider the level of quaternary prevention [139]. Due to the clinical implications, the technology focused on the obtaining, processing and analysis of images from the fundus; among those that are the slit-lamp, fundus cameras, fundus fluorescein angiography (FFA), indocyanine green angiography (ICG), fundus autofluorescence (FAF), optical coherence tomography (OCT) [140,141].

Table 8: Problematic axes circumscribed to DR prevention levels

Level of Prevention	Scope of Prevention	Problematic Axes
Primary	Health promotion	Computer models to assess general and specific life risks.
	Specific protection	Non-invasive screening for the identification of retinal lesions.
Secondary	Diagnosis	Obtainment, analysis and processing of retinal images. Obtaining, analyzing and processing retinal bioelectrical signals.
	Treatment	Design of biomaterials, as well as devices for the administration and intraocular release of drugs.
Tertiary	Rehabilitation	Design and development of visual prostheses, retinal implants and implantable microelectrodes.
Quaternary	Avoid therapeutic derision	Computer models.

For the field of the installation and evolution of the DR, it is of special importance the evaluation of the blood flow of the retinal vessels, with the possibility of analyzing the layers of the vessels in patients with DM, for which angiography is very useful by OCT [142].

Advances in the development of new drugs for the treatment of DR, as well as the need to assess the long-term effect produced by therapeutic interventions in the patient, expose the need to identify biomarkers that also make it possible to guide the diagnosis of disease as well as the forecast of it [143,144]. Cunha-Vaz et al [145], recognize different biomarkers to evaluate the installation, progression and prognosis of DR; among these are: genetic biomarkers, microaneurysm turnover, subclinical macular edema, early functional changes in multifocal electroretinography, and percentage of decrease in the thickness of the central retina. For the identification and analysis of biomarkers, angiographic optical coherence tomography (OCTA), retinal oximetry, ultra-wide field FA, and cofocal corneal microscopy (CCM) are being used [146].

In 1946, Michalko [147] reflected on his experience with blind patients, developing his ideas in two ways: the search for scientific explanations for the alterations in vision and quality of life of the patient during blindness. On the one hand, it explores the mystery of being, of having a condition that marginalizes, excludes and segregates the human being in the process of sharing and living with others in the world of life. And on the other, it stops before the suffering of knowing itself in the world on which a different reality is constructed, starting by perceiving it differently. In this context, the problematic fields of interest for Medical Bioengineering converge in philosophical reflection, whether in the ontological (of being), the ethical (of doing) or the epistemological (of knowing); so that the fields listed above are added to the fields of philosophical inquiry (table 9).

Table 9: Problematic axes of philosophical interest for DR

Philosophical Domain	Problematic Axes
Ontological	Analysis of the causal relationships in the progression of DR. Reflection of the conception of the human being with visual prostheses.
Ethical	Implications of the development of technological tools in telemedicine.
Epistemological	Analysis of the logic of teleological research in the construction of the scientific meta-report for the transdisciplinary dialogue in the understanding of DR. Development of strategies to transfer the advances of biomedicine, to the treatment of the patient with DR.

IV. Conclusion

DR is the most frequent microvascular complication of DM, and as the incidence of DM increases, DR becomes a public health problem of social, cultural, anthropological, economic and philosophical interest, because it affects the fundamental sense in the perception of the world of life. In this sense, it is essential to understand the pathophysiology of DR to identify the possibility of participation of the Medical Bioengineer in the containment of this health problem.

The pathogenesis starts early with homeostatic alterations of glucose, which induces an inflammatory response that will affect the perfusion of oxygen and increase the concentration of pro-inflammatory substances, producing inflammation, apoptosis of pericytes and finally the microvascular damage of the retinal vessels will be installed. Subsequently, microaneurysms, retinal hemorrhages, and thickening of the retinal basement membrane will develop, which will evolve towards retinal edema and retinal detachment, installing diabetic macular edema.

In the pathophysiological progression of DR, inflammatory processes have acquired relevance at the molecular level, expanding the level of understanding of the alterations in vision that in their natural evolution

will progress to the loss of the sense of sight.

As mentioned above, many ongoing studies are investigating the possibility of early detection of DR. Even in very recent literature, there is no definite and reliable connection of changes in the retinal vasculature and the development of DR. Until recently, it was impossible to take measurements of oxygen saturation in vessel segments accurately and reliably. In recent years it has been possible to study the oxygen saturation in the retinal vasculature, make precise measurements and at the same time investigate whether the deterioration of oxygen perfusion precedes or follows the development of DR. A great challenge and another important observation are the autoregulatory responses of the retinal vasculature to the altered hemodynamic function, which is not yet clear how it is altered in relation to the disease. In addition, there could be some progress in understanding whether the final positions of the lesions in the vasculature are random or if they are determined by other factors and if there is any change in the position of the vessels before the lesions finally appear in this specific area.

As can be seen, the different approaches for the delimitation of problematic fields are converging in the internationally recognized disciplines of Medical Bioengineering, although new areas of knowledge are gradually being incorporated, oriented towards the health care of patients with DR; so that the delimitation of problematic fields makes it possible to explore the complexity of DR, however, the study conducted has limitations related to the number of publications related to DR.

Finally, it is concluded that the DR is being constructed as a research program of the Lakatosian type, since it shows a sequential set of scientific theories, which have the possibility of expressing themselves in spatio-temporal relations of the developing knowledge, as well as the researchers scientists involved in the study of DR. The hard core concentrates the scientifically and socially accepted knowledge of DR, which through the natural history of the disease concentrates on theories of vascular damage and neuronal damage to explain the pathogenesis and pathophysiology, both in the prepatogenic period, as well as in the installation and progression of the DR. In the protective belt hypotheses have been located that are configuring the neurodegenerative theory induced immunologically linked to the etiopathogenesis, installation and progression of DR; so that the identification of problematic fields both disciplinary and at the level of the stages of the natural history of the disease as well as the levels of prevention, provide a space-time direction to the task of the Medical Bioengineering, mainly in areas of attention to the health of the patient with DR. Special mention acquires the development of problematic fields in the scope of philosophy, specifically that of epistemology, given its importance for the critical analysis of scientific meta-discourse.

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