

## **Diabetic retinopathy, prevention and treatment on the Brazilian public health system: a literature review**

### **Retinopatia diabética, prevenção e tratamento no sistema público de saúde brasileiro: uma revisão da literature**

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#### **ABSTRACT**

This study aimed to elucidate the diagnosis of diabetic retinopathy, to show the importance of early diagnosis in primary services and to point out the misinformation of patients about it. A systematic review was made in the databases Scielo, PubMed and Lilacs, selecting 32 articles from the last 11 years. The diabetic patients' misinformation on this condition is high, getting up to 76%. Also, most primary health services do not make exams such as funduscopy, so the patients only discover the disease when losing visual acuity. Implementing the knowledge and the funduscopy to these professionals can provide an early tracking of cases, decreasing the irreversible blindness through early treatment, avoiding greater suffering and sparing public money by preventing, instead of treating it.

**Keywords:** diabetic retinopathy, fundus oculi, diabetes complication, diabetes mellitus complication, primary prevention.

#### **RESUMO**

Este estudo visou elucidar o diagnóstico da retinopatia diabética, mostrar a importância do diagnóstico precoce nos serviços primários e apontar a desinformação dos pacientes a esse respeito. Foi feita uma revisão sistemática nas bases de dados Scielo, PubMed e Lilacs, selecionando 32 artigos dos últimos 11 anos. A desinformação dos pacientes diabéticos sobre esta condição é alta, chegando a 76%. Além disso, a maioria dos serviços de saúde primários não fazem exames como a fundoscopia, portanto, os pacientes só descobrem a doença quando perdem a acuidade visual. A implementação do conhecimento e da fundoscopia para estes profissionais pode proporcionar um acompanhamento precoce dos casos, diminuindo a cegueira irreversível através de um tratamento precoce, evitando maior sofrimento e poupando dinheiro público ao prevenir, ao invés de tratá-lo.

**Palavras-chave:** retinopatia diabética, fundus oculi, complicação do diabetes, complicação do diabetes mellitus, prevenção primária.

## 1 INTRODUCTION

Diabetes mellitus (DM) is a disease with high prevalence, which should double its occurrence in the next 20 years. One of the complications is diabetic retinopathy (DR), a cause for visual impairment. The need to approach this complication in a preventive way is in order to reduce the costs and the crowding of health care systems all over the world<sup>1</sup>. In a research that was conducted at the *Universidade de Campinas* (UNICAMP), the DR corresponded to up to 33% of the cases of low acuity<sup>2</sup>. Among the risk factors there are: disease's duration (over 20 years), patient's age, the associated higher blood pressure and the inadequate glycemic control<sup>3</sup>. There is a genetic factor, by which there is an increased risk of severity of the DR in family members<sup>4</sup>. A few inflammatory markers and proteins are involved, and others are being investigated, such as the metabolomics and micro-RNA<sup>5</sup>.

The main goal of this review is to elucidate the clinical condition of DR, its ways of diagnosing to assist all medical specialties, assess the need of its tracking in primary health care and guide unoriented patients about it.

## 2 METHODS

Scientific articles were searched in databases such as Scielo, PubMed, Lilacs and Google Scholar, with the descriptors “diabetic retinopathy”, “review”, “pathophysiology”, “treatment” and “diabetic retinopathy in the primary care” in the last 20 years. The excluded files were those that cited pharmaceutical companies, the repeated ones, the ones that did not fit the subject and the paid ones. In total, we found over 500 articles and selected 32 of them, from 2011 to 2022.

## 3 RESULTS

A transversal study took place in Goiânia (Goiás, Brazil), in 2018, with 219 patients with DM, and showed that 31% presented DR in different stages, at an age of 50 to 70 years or with over 10 years of disease. There is higher incidence in patients with Body Mass Index (BMI) above 40. Besides, the practice of physical activities was related to not developing DR<sup>6</sup>.

It is important to get this knowledge to the patients, since 76% of them have none about the disease. A study in Roraima (Brazil) with 150 diabetics, in the *Sistema Único de Saúde* (SUS), shows that 40% never got any type of orientation about the risk of visual loss, emphasizing the importance of primary health care doctors and specialists giving instructions to their patients<sup>7</sup>.

#### 4 DISCUSSION

The inflammatory mediators from DM modify the retinal function, being the first alterations in the electroretinogram the failing in vascular flow's self-regulation, detected before clinical signs<sup>8</sup>.

The tissue stress caused by hyperglycemia stimulates the microglia, which becomes reactive, produces pro-inflammatory cytokines and chemokines causing chronic inflammation, development and progression of DR<sup>9</sup>. The vascular endothelial growth factor (VEGF) is a cytokine that acts through receptors expressed in the vascular endothelium, increasing the permeability and neovascularization. It is increased in the aqueous humour and the vitreous of patients with DR, mainly in the proliferative type (PDR)<sup>10</sup>.

The nitric oxide (NO) is a vasodilator and the hyperglycemia reduces its production<sup>5</sup>. The dimethylarginine is an endogenous inhibitor of the NO-synthase and when it increases, the NO synthesis decreases, causing endothelial dysfunction and reduction of subfoveal choroidal depth in patients with DM 2<sup>11</sup>.

The oxidative stress is caused by the excessive elimination of oxygen reactive species (ORSs), contributing and being the result of metabolic abnormalities induced by hyperglycemia. Its accumulation causes mitochondrial damage, cell apoptosis, inflammation, lipid peroxidation and structural and functional alterations in the retina. This allows many new and safer therapeutic targets<sup>12</sup>.

Recently, it has been discovered the role of DR in neurodegeneration, suggesting a biomarker as early as vasculopathy. An oxidative stress is formed through the breaking of glucose and lipidic state, forming advanced products in glycation, an inflammatory state, suppressing neuroprotective pathways and inducing damage to DNA and apoptosis. The studies about substances that attenuate this inflammatory state are mainly in antioxidants, neuroprotective and anti-inflammatory factors<sup>13</sup>.

The DM also affects the retina tissue-specific control of lipid remodeling and elimination, such as such as cholesterol, fatty acids, triglycerides, total cholesterol and it

elevates LDL, inhibits HDL and worsens the clinical condition by providing macular edema and retinal vascular degeneration<sup>14</sup>.

The PDR is the neovascularization of the retina and optic nerve, occurring in later stages, secondary to micro occlusion and vascular ischemia<sup>1</sup>.

Most patients with DR do not have any symptoms until the appearance of macular edema or PDR. This is why programs of screening could help maintain vision<sup>5</sup>.

The small lesions in the fundus, the ballooning of the capillaries, are the microaneurysms and hemorrhagic spots. The exudates are formed by heavy lipoproteins left by the reabsorption of the edema caused by hemorrhage and leakage of liquid. Hemorrhagic spots occur in occluded capillaries, frequently associated with cotton wool spots, in neuronal infarctions caused by a disturbed axoplasmic flow. And the microvascular anomalies, caused by the attempt to remodel ischemic areas<sup>15</sup>.

The investigation is done through color retinography, which has low cost, it is not invasive and easily implemented. Fluorescein angiography is reserved for selected cases, assisting in classification and managing of already diagnosed patients<sup>16</sup>.

The golden standard for PDR diagnosis is stereoscopic fundus photography and fluorescein angiography. Recently, optical coherence tomography is gaining space in diagnose of neovascularization and microaneurysms<sup>17</sup>.

The diagnosis can also be done through artificial intelligence, using deep learning, exceeding a 90% rate of specificity and sensibility. By not considering all aspects that are specific and personal to each patient, it can be used as a “second opinion”<sup>18 19</sup>.

In retinopathy, a fundoscopy is necessary, but in rural regions that do not have specialists, the population is unassisted. With the Covid-19 pandemic, several segments were affected but telemedicine increased its coverage and in DR it is used as glycemic monitoring by electronic devices, cameras or other portable devices that allow many different professionals to photograph the fundus and send it to specialized centers. Although there is a high initial cost in obtaining devices and training people, with time, it provides significant money saving<sup>20 21</sup>.

The United Kingdom was the first country to have a screening program for DR, and in 2008 it already had covered the whole territory and because of it, DM stopped being the main cause of visual loss<sup>1</sup>.

Among the differential diagnosis, there is ocular ischemic syndrome caused by chronic ocular hypoperfusion, internal or common carotid stenosis, with visual loss and ocular pain. There are also uveitis, iris neovascularization, vasodilation and intraretinal

hemorrhage. With this, if there is a very asymmetric proliferative retinopathy or refractory to the treatment, it should be made an investigation to the carotid arteries flow<sup>22</sup>.

Among the complications there is the vitreous hemorrhage, which can cause an important reduction in visual acuity and the tractional retinal detachment, leading to an important visual loss, which is an indication of surgery. In non-proliferative there is the macular edema or the retinal thickness<sup>23</sup>.

The first line of treatment is intravitreal with anti-VEGF drugs, lasers or steroids (dexamethasone or fluocinolone implants). The last one is mainly used in cases with chronic edema that was not very responsive to other therapies<sup>1</sup>. In the eyes of patients with not high risk RDP, the panretinal photocoagulation plus ranibizumab causes less sensibility damages to contrast, if compared to isolated panretinal photocoagulation<sup>24</sup>.

The use of intravitreal injection of ranibizumab isolated or associated with ETDRS (*Early Treatment Diabetic Retinopathy Study*) or PASCAL (*Pattern Screening Laser*, Topcon, Santa Clara, CA) panretinal photocoagulation presents resemblance in the improvement of visual acuity, central subfield thickness and decrease of active neovessels<sup>25</sup>. The use of intravitreal ranibizumab or panretinal photocoagulation, to PDR is similar and good in both groups. Although there are very small differences, anti-VEGF therapy and photocoagulation are viable treatments with good results for proliferative DR<sup>26</sup>.

The laser photocoagulation reduces the ischemic tissue area in the retina, becoming an important pillar to SUS users, because there is a considerable lack of access to intravitreal antiangiogenic therapy<sup>27</sup>.

The use of erythropoietin, well widespread in ophthalmology, is not efficient in this case because angiogenesis is one of its side effects<sup>28</sup>.

In pregnant women, the glycemia and ingestion of sugar are controlled. The use of laser and intravitreal steroids is preferable in the second and third trimesters<sup>29</sup>. In the elderly, it is taken in consideration the ocular alterations caused by age, decrease of oral medical absorption and bad adhesion, more than in young patients<sup>30</sup>.

The risk of disease's progression decreases up to 40% when it is associated with physical activities and nutritional education<sup>31</sup>. The tracking is recommended by the Brazilian Society of Diabetes after the diagnosis of DM2, with an immediate ophthalmological appointment. In patients that have DM1, it can be up to 5 years after the diagnosis or after the beginning of puberty. The promotion of activities with the

population can serve as an active tracking of DR as well as working on this prevention alerting the population<sup>32</sup>.

In visual deficiency patients' rehab are done multidisciplinary care, which helps dealing with loss, potentializes the abilities to independent development and autonomy in everyday activities<sup>2</sup>.

## **5 CONCLUSIONS**

The DR is an important cause of blindness in the world, specially by being related to a chronic disease that has high incidence and prevalence in Brazil, which is the DM in all of its kinds. With a universal health system, it is more and more necessary to guide professionals so that they can also guide their patients about the need of regular checkups with an ophthalmologist or even capacitating professionals of primary care so that they can, in routine appointments, observe through funduscopy suggestive alterations and refer them to a specialist. Then there will be a more enlightened and vigilant population, with early diagnosis that can improve the visual acuity, avoiding greater suffering and more expenses with complications of DR.

This means it is necessary to implement the knowledge and the funduscopy to the basic health unities professionals, so they can be able to provide an early tracking of DR cases, decreasing the irreversible blindness through early treatment. Also, by implementing this vigilance, one can give the patients a better life quality, improving their independency in daily activities and productivity, in addition to bringing the patient closer to the doctor and increasing empathy and trust among them.

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