DIABETIC RETINOPATHY: A SYSTEMATIC REVIEW OF DEVELOPMENTAL FACTORS IN ADULTS TREATED IN PRIMARY HEALTH CARE

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ABSTRACT

Diabetic retinopathy (DR) is one of the main microvascular complications of diabetes mellitus, being a common cause of irreversible vision loss in adults. DR affects about one-third of diabetics, with a progression divided into nonproliferative and proliferative stages, with complications associated with retinal neovascularization. PHC plays a crucial role in prevention and early diagnosis, however, it faces challenges such as lack of infrastructure, lack of ophthalmologists in primary care, and difficulties in articulating between the levels of care of the Unified Health System (SUS). Factors such as low socioeconomic status, advanced age, presence of comorbidities, and longer time since diagnosis are determinants in the development of DR. Therefore, this study seeks to contribute to the understanding of risk factors and improve care strategies for this population. Thus, it is a systematic review of the literature, of an observational, qualitative and cross-sectional nature. The search was

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based on the Lilacs (Latin American and Caribbean Literature on Health Sciences), PubMed (US National Library of Medicine National Institutes of Health), SciELO (Scientific Electronic Library Online), EMBASE, Scopus and Science Direct databases, using the search terms "Diabetes Mellitus", "Diabetic Retinopathy", "Primary Health Care", and their synonyms. In all, six articles were reviewed. The analysis of the studies was organized into two categories: one that evaluated the structure of the health system and the patient's social issue, and the other that included physiological aspects involved in the development of DR. Thus, it was observed that the evolution of diabetic retinopathy in Primary Health Care is related to multidimensional factors, such as the absence of DR screening and poor metabolic control.

Keywords: Diabetic Retinopathy. Diabetes Mellitus. Primary Health Care. Systematic Review.

INTRODUCTION

Diabetes mellitus, when at high and persistent levels, not controlled by the patient, can cause acute complications, such as diabetic ketoacidosis, or chronic complications, which can be divided into macrovascular (coronary artery disease, cerebrovascular and peripheral vascular disease) or microvascular alterations, such as diabetic retinopathy, peripheral neuropathy and diabetic nephropathy (FONSECA and ABI RACHED, 2019).

The main microvascular complication is diabetic retinopathy (DR), which is one of the most common causes of irreversible vision loss in the population between 16 and 64 years of age worldwide (GALVÃO *et al.,* 2021). It affects about a third of people with the disease and it is estimated that 50% of carriers will develop some degree of retinopathy throughout their lives (HIRAKAWA *et al.,* 2019).

In Brazil, approximately 13 million people have it and there are estimates of 4 million cases due to DR. This ocular alteration also implies economic losses, since the cost of losing productivity for someone who has lost their vision is about 5 times higher than the costs of health care (GALVÃO *et al.,* 2021).

DR has two stages, an initial one, called non-proliferative and a more advanced one, called proliferative (WANG and LO, 2018). The difference consists precisely in the process of retinal neovascularization present in proliferative diabetic retinopathy (PDR). The first signs of this more advanced stage can be observed in the ocular fundoscopy exam, in which micro aneurysms, hemorrhages and edema are found. Visualization of the formation of neovessels implies the diagnosis of PDR (TANURI *et al.,* 2023).

Regarding the pathophysiology of the disease, there are a number of complex reactions involving angiogenesis and apoptosis of retinal blood vessels. Blindness occurs when excess glucose induces the development of edema, microaneurysms, exudates, venous dilatations, and neovascularization in the retinal tissue (KUMAR; ABBAS; ASTER, 2013).

Follow-up at the Primary Health Care (PHC) level is aimed at preventing or early diagnosing complications of diabetes mellitus, such as DR (ALVES *et al.,* 2014). However, there are many challenges to this end, which can occur extrinsically or intrinsically to patients (PASINI; BERBIGIER; SCHUCH, 2022).

As in the former, there is the lack of adequate structure, as well as the deficiency of articulation between the health network, lack of trained professionals, since the Unified Health System (SUS) places ophthalmologists at the secondary or tertiary level of care, in

addition to the small amount of inputs that favor adequate diagnosis and therapy (PASINI; BERBIGIER; SCHUCH, 2022).

The elements inherent to carriers of the disease, in turn, are represented by conditions that can favor the development of complications, such as lower socioeconomic and educational level, male gender, advanced age, presence of associated comorbidities, and longer time of diagnosis (DE ALMEIDA *et al.,* 2024).

In view of this scenario, the objective of this study is to identify the factors related to the onset and development of diabetic retinopathy in patients with diabetes mellitus treated in Primary Health Care.

METHODOLOGY

This is a systematic review of the literature. Thus, a secondary and retrospective research that aimed to gather in an organized and summarized way the best scientific evidence on the researched theme, from data extracted from original articles through an objective and critical analysis.

The proposal of Donato and Donato (2019) was followed, carrying out the research in nine ordered stages: 1) Elaboration of the question; 2) Production of the investigation protocol; 3) Definition of inclusion and exclusion criteria; 4) Development of the search strategy; 5) Selection of studies; 6) Critical analysis of the quality of the studies; 7) Data extraction; 8) Synthesis of knowledge; 9) Publication. The PRISMA checklist was followed to help report the main items of systematic reviews.

The PICo strategy (TAKAHASHI; SAHEKI; GARDIM, 2014) and the following research question was elaborated: "What factors are related to the appearance and development of diabetic retinopathy in adult patients treated in Primary Health Care?"

Once created, the search protocol was submitted to the PROSPERO (International Prospective Register of Systematic Reviews) platform and received the identification number CRD42022363857.

Original, complete articles published in national and international journals between 2017 and 2021, written in Portuguese, Spanish, or English, were searched. Searches were carried out in September and October 2022 in six databases: Lilacs (Latin American and Caribbean Literature on Health Sciences), PubMed (US National Library of Medicine National Institutes of Health), SciELO (Scientific Electronic Library Online), EMBASE, Scopus, and Science Direct.

In the searches, the descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH) were used. The DeCS in Portuguese were: "Diabetes Mellitus", "Diabetic Retinopathy", "Primary Health Care", and their synonyms. The MeSH in English were: "Diabetes Mellitus", "Diabetic Retinopathy", "Primary Health Care", "Eye Screening" and "Diabetic Eye Disease".

The following inclusion criteria were used: complete and free articles with reports of original research carried out with people over 18 years of age with diabetes mellitus, regardless of gender; that brought factors related to the appearance and development of diabetic retinopathy; referring to care at the level of Primary Health Care.
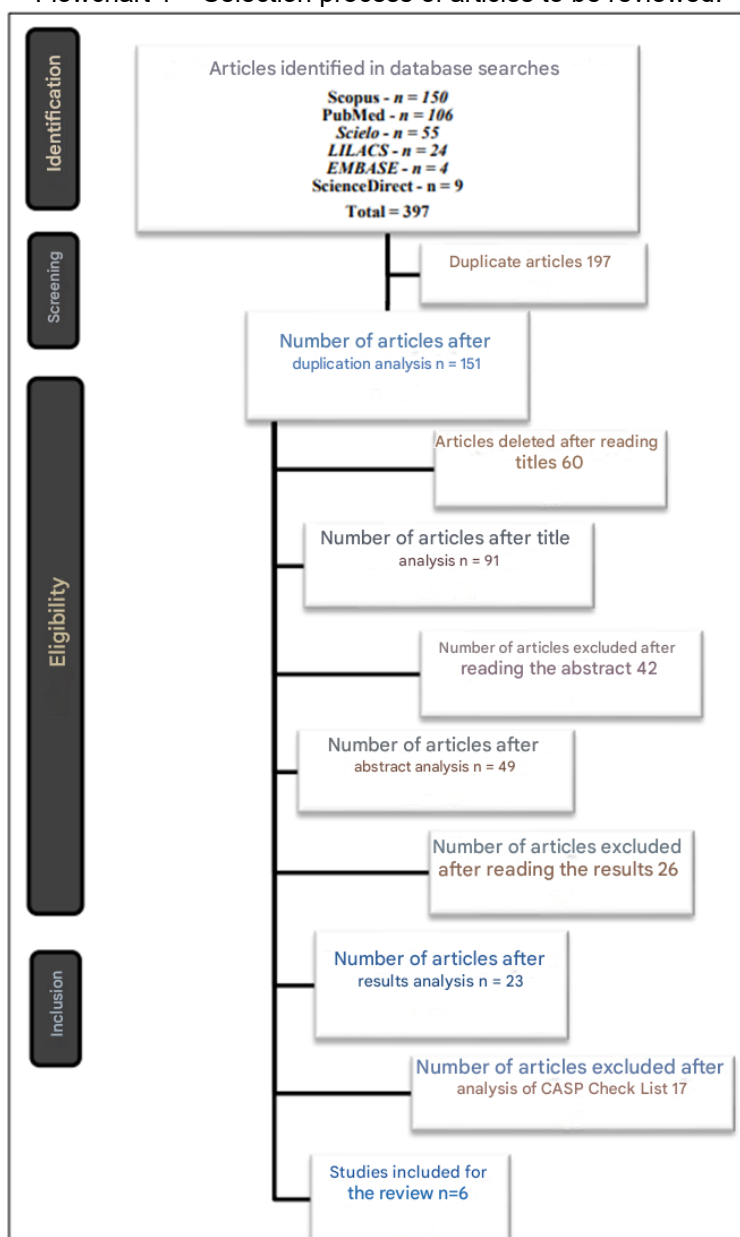
On the other hand, articles with research reports that are not available with their full text or for a fee and without sufficient coverage of the proposed theme were excluded. Editorials, opinion articles, review studies, theses, dissertations, course completion papers, books and book chapters were also excluded.

The Rayyan app was used to assist in the exclusion of duplicates and the CASP (Critical Appraisal Skills Programme) checklist was used to assess the quality of the evidence and the strength of the recommendations. To avoid bias, the articles selected for full reading were independently analyzed by two authors. Finally, the data obtained were arranged in tables in Microsoft Excel and written in Microsoft Word, for better organization of the work.

RESULTS

From the searches in the six databases, 348 articles were identified, as can be seen in Flowchart 1. Through the Rayyan application, 197 duplicates were discarded, leaving 151 studies to be read by their titles, abstracts and results. Only 23 articles were selected to be read in full, but after applying the CASP checklist, 6 articles were included for analysis in this work.

Flowchart 1 – Selection process of articles to be reviewed.

Articles identified in database searches
Scopus - *n = 150*
PubMed - *n = 106*
Scielo - *n = 55*
LILACS - *n = 24*
EMBASE - *n = 4*
ScienceDirect - n = 9
Total = 397

Duplicate articles 197

Number of articles after
duplication analysis n = 151

Articles deleted after reading
titles 60

Number of articles after title
analysis n = 91

Number of articles excluded after
reading the abstract 42

Number of articles after
abstract analysis n = 49

Number of articles excluded
after reading the results 26

Number of articles after
results analysis n = 23

Number of articles excluded after
analysis of CASP Check List 17

Studies included for
the review n=6

Identification | Screening | Eligibility | Inclusion

Source: prepared by the authors, 2024.

The six articles reviewed in this study come from research conducted in six different countries: Australia, Cuba, Chile, China, the United States of America, and Palestine.

Table 1 provides general information on the items included. All presented international research results. Two are published in Spanish and four in English. The sample includes analytical studies, qualitative research, and epidemiological studies.

Chart 1 – Description of the seven studies included in the review, according to country of conduction, method and main results.

Author, Year and Country	Journal and Title	Method

WATSON et al., 2021 Australia	BMC Family Practice Barriers and facilitators to diabetic retinopathy screening within Australian primary care	• Qualitative study. • Semi-structured interview conducted by telephone. • 15 general practitioners participated; included from the use of the snowball technique.
YAHYA et al., 2020 Palestine	Journal of Diabetes & Metabolic Disorders Diabetic retinopathy screening barriers among Palestinian primary health care patients: a qualitative study	• Qualitative study. • Three focus groups with a total of 24 patients with diabetes who had never been screened or their last test for DR occurred more than 18 months ago. • Participants were recruited by telephone or contacted by their family doctor.
BURSELL et al., 2018 USA	Plos ONE Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for American indians and alaskan natives	• Multicenter, clinical, epidemiological and retrospective study • Retrospective analysis of data from 53,998 patients evaluated between 2011 and 2016 by the IHS-JVN (teleophthalmology program of the Indigenous Health Services).
COVARRUBIAS et al., 2017 Chile	Medical Journal of Chile Screening in the diagnosis and prevalence of diabetic retinopathy in primary care	• Epidemiological and retrospective study • Conducted with 9,222 patients with diabetes between January 2014 and June 2016. • Participants living in urban and rural areas, beneficiaries of the SSMSO (public service-private health care).
MARTÍNEZ et al., 2020 Cuba	Multimed (Granma) Prognostic value of glycated hemoglobin HbA1c in diabetic retinopathy in patients with type II diabetes mellitus	• Cross-sectional analytical study • 181 patients diagnosed with type II diabetes mellitus who were divided into a study group and a control group. • Each patient was followed up for two years and three glycated hemoglobins were performed, three fasting blood glucose and two ophthalmologic controls.
HU et al., 2021 China	Endocrine Practices A Higher Serum Calcium Level is an Independent Risk Factor for Vision- Threatening Diabetic Retinopathy in Patients with Type 2 Diabetes: Cross- Sectional and Longitudinal Analyses	• Cross-sectional and longitudinal cohort study • The cross-sectional part included all patients treated for T2DM in primary care between 2007 and 2016. The longitudinal part involved an overlapping cohort study of patients with diabetes without proliferative diabetic retinopathy who were followed from their admission until December 2019.

Source: prepared by the authors, 2024.

Chart 2 – Distribution of the reviewed articles into two categories and main results.

Category	Author	Main results
	WATSON et al., 2021	Staff training, lack of equipment and government assistance, and time constraints were factors that contributed to greater difficulty in performing HR screening in Primary Care.

1 Social issue and structure of the health system	YAHYA et al., 2020	The following were identified as barriers to DR screening: Structure of the health system: difficulty in getting appointments, long waiting time, lack of adequate places and ophthalmologists. Social and cultural issues: financial condition, fear of the test result, negative experiences of other family members, stigma of wearing glasses, lack of knowledge of DR and its treatment.
	BURSELL et al., 2018	The prevalence was lower in Alaska and higher among patients with A1c >/ = 8%, duration of diabetes > 10 years, or using insulin. Percentages found of non-proliferative DR 17.7%, proliferative DR 2.3%, diabetic macular edema 2.3%, retinopathy with threat to vision 4.2%. These data point to a decreased incidence of DR among participants, possibly due to better diabetes control.
	COVARRUBIAS et al., 2017	According to the demographic variables of the patients included in the Cardiovascular Health Program (CVP), there is no significant difference in diabetic retinopathy according to sex (female and male). This difference was only 0.8% with nonproliferative diabetic retinopathy and 1% with proliferative diabetic retinopathy. On the other hand, in urban areas, the percentage of diabetic retinopathy in both modalities (proliferative and nonproliferative) is about 32.4% higher than in rural areas.
02 Physiological factors of DR evolution	MARTÍNEZ et al., 2020	An incremental relationship was observed for the risk of diabetic retinopathy according to the ascending level of glycated hemoglobin based on the increase in the associated risk trend for diabetic retinopathy, from almost double with HbA1c values between 7.1 and 8.0 to more than triple when HbA1c values were equal to or greater than 10.1.
	HU et al., 2021	The cross-sectional analysis included 3,269 patients. Serum calcium, younger age, longer duration of diabetes, albuminuria, impaired renal function, and low serum magnesium were independently associated with DR. In the longitudinal analysis, 649 patients were included. 95 individuals developed diabetic retinopathy with risk of vision loss. The following were identified as independent risk factors for vision loss due to DR: high serum calcium, younger age, longer duration of diabetes, albuminuria, lower serum magnesium, and higher glycated hemoglobin.

Source: prepared by the authors, 2024.

The first category included two qualitative studies and two epidemiological studies. The composition of the surveyed samples and survey methods varied between these studies. Regarding the two studies with qualitative methodology, in one focus groups were held with patients, while in the other, semi-structured interviews were conducted with general practitioners. Among the results, structural issues of the health systems were found, as well as social and personal elements of the patients, such as financial condition and fear of the test result.

Regarding epidemiological studies, both are retrospective and were based on data obtained from PHC consultations, one being carried out in Chile and the other in the USA. The results do not show a significant difference between the sexes, but there are relevant

differences between residents of urban and rural regions. Better diabetes control may be related to a decreased incidence of DR.

The second category includes research that addressed physiological aspects involved with the evolution of DR. This group contains two articles, both analytical studies, one cross-sectional and the other with a mixed method: with cross-sectional stage and longitudinal cohort stage. The results indicated a high risk of developing DR when there are high levels of glycated hemoglobin. Younger age, long duration of diabetes, high serum calcium, and lower serum magnesium have been identified as independent risk factors for vision loss due to DR.

DISCUSSION

SOCIAL ISSUE AND STRUCTURE OF THE HEALTH SYSTEM

There is evidence that an increase in DR screening results in a decrease in the rates of progression to more severe clinical conditions, with a risk of vision loss (KURIAN *et al.,* 2021). What helps to explain this fact may be the duration of diabetes associated with poor follow-up, in this sense, the later DR is diagnosed and treated, the greater the chance of evolution occurring, as pointed out by Covarrubias et al. (2017).

For the implementation of an efficient DR screening program, staff training is an essential issue (KHOU *et al.,* 2021). In more specialized care services, this fact is not so expressive. However, when it comes to Primary Health Care – especially when thinking about rural areas, where the lack of access to ophthalmologists and optometrists coexists with the lack of structure, demonstrated in the

lack of material and equipment, such as retinal cameras, essential for a good diagnosis of DR – DR screening is extremely difficult (WATSON *et al.,* 2019), which explains the higher incidence of DR with risk of vision loss in populations in these areas.

In addition, there are still social issues that directly impact the evolution of HR. The absence of health education about a particular disease and its prevention and control strategies often distances the patient from a possible screening, this added to financial and, in some cases, religious issues, impact on low adherence to DR screening (YAHYA *et al.,* 2020).

In addition, there is disparity in terms of adherence to treatment between females and males. According to Covarrubias *et al.* (2017), about 61.5% of the patients included for screening in PHC for diabetic retinopathy were women, and only 38.5% were men. In this

sense, there is speculation about the reproduction of behaviors and practices aimed at health care among men and women, in which there is a greater responsibility and concern on the part of them for the monitoring of the pathology (KOLCHRAIBER *et al.,* 2018).

PHYSIOLOGICAL FACTORS OF DR EVOLUTION

In addition to socioeconomic and structural factors, there are several physiological factors that contribute to the development of diabetic retinopathy and that are the focus of study in the literature. Among the articles that were included in the results of this research, the following biochemical factors were evidenced: glycated hemoglobin (HbA1c), the RAGE-374T/A polymorphism and serum calcium.

The article by Martínez et al. (2020) carried out an investigation in which a linear incremental risk relationship for glycated hemoglobin (HbA1c) values greater than 7% was found with the onset of diabetic retinopathy in patients diagnosed with type 2 diabetes mellitus.

Other studies that investigated this same factor obtained similar results, such as the one carried out by Miranda *et al.* (2021) with people with type 2 DM, in which retinopathy progression was associated with HbA1c values above 7% in 90% of patients in the case group and 61.7% in the control group.

In addition, Mjwara et al. (2021) analyzed HbA1c levels in groups of patients with type 1 and type 2 diabetes, in which patients with RDP had significantly higher HbA1c levels than those without DR, in addition patients with type 1 DM had higher HbA1c levels than those with type 2 DM in both groups, RDP and no RD.

Regarding poor metabolic control, the increase in serum calcium levels is directly proportional to the progression in the stages of DR. According to HU *et al.* (2021), in a group of 3,269 patients, among the group of people with the highest serum calcium levels, the prevalence of diabetic retinopathy was 26.8%. Thus, it is noted that the lack of follow-up of serum calcium ion balance in patients with DR can lead to a more severe condition of the disease and, therefore, possibly to early loss of vision.

Furthermore, the research by Yanan Hu *et al.* (2021) obtained a similar result, as it associated the molecular increase in serum calcium and the prevalence of diabetic retinopathy in a PHC, and of the 649 patients analyzed, 95 of them developed diabetic retinopathy with risk of vision loss, even during the follow-up of the research.

CONCLUSION

The evolution of diabetic retinopathy in Primary Health Care is related to multidimensional factors, ranging from the structure of the health system to social, cultural, and physiological issues. In health care, the absence of DR screening or its inefficiency proved to be one of the main causes for the progression of the disease.

The development of DR is related to the lack of early detection of biochemical agents, as reported in this study, and also to poor metabolic control expressed by high levels of glycated hemoglobin, which are also directly associated with the risk of developing DR. Thus, from this systematic review it was possible to verify the association of multiple physiological, technical, structural and organizational factors of health systems that impact the appearance and development of diabetic retinopathy in Primary Health Care.

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