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RESEARCH ARTICLE

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RETINOPATHY AS A BIOMARKER OF MORBIDITY IN PEOPLE WITH DIABETES MELLITUS

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ABSTRACT

The aim of the study was to identify biomarkers of morbidity in people with diabetic retinopathy (DR). This is an integrative literature review of studies addressing DR as a biomarker of morbidity. Full studies published between 2010 and 2020 in English, Spanish and Portuguese languages were included. The search was conducted in the VHL, PubMed and ScIELO databases, using morbidity, biomarkers and diabetic retinopathy as descriptors. Six articles were selected, corresponding to the objective of the study. Despite the diversity of biomarkers indicating morbidity in people with DR, it was found that the research findings were similar, four referring to macrovascular complications and two about microvascular complications. The close relationship between DR and these complications, showed that damage to the retinal microvasculature and its progression leads to the development of complications, which can be screened using predictive biomarkers of morbidity, thus reducing the high indicators of diabetes morbidity and mortality.

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INTRODUCTION

Diabetes Mellitus (DM) is considered a global health challenge, with the fastest growth in the number of affected in recent years, and despite the clinical and public health interventions, the future projections point to an increase in its prevalence. In 2019 the global prevalence of people living with the disease was 9.3% among adults aged 20-79 years, representing 463 million cases. In that same year, it was observed that 16.8 million adults and 6.1 million elderly people with diabetes in Brazil, taking the country to fifth place in the world ranking in both age groups (IDF, 2019). In view of the growing prevalence of people with DM, especially in underdeveloped countries such as Brazil, the risk of these individuals developing complications related to the disease is perceived, which contributes to the increase in morbidity and mortality indicators. Furthermore, they have a negative impact on people's survival, due to the need for frequent hospitalizations caused by poor management of risk factors, which generates high costs with treatments, reduced quality of life and unproductiveness, directly affecting socioeconomic conditions

and the access to health services (IDF, 2019). Diabetic Retinopathy (DR) is one of the main and most common complication of DM, being also the main cause of blindness in people living with the disease. It is a microvascular complication resulting from vascular and neural damage, which represents a high risk for the development of other vascular complications, especially macrovascular ones that result in neural damage, including peripheral and autonomic neuropathy and cardiovascular diseases (ONDREJKOVA *et al.*, 2019; SIMÓ-SERVAT; HERNÁNDEZ; SIMÓ, 2019; JENKINS *et al.*, 2015). Taking into consideration that future projections indicate a progressive increase in people with DR, possibly this complication will become an even more serious public health problem. Therefore, analyzing DR as a complication that affects the retinal microvasculature and for being the most common among people with DM, it configures itself as an important biomarker to track other possible morbidity biomarkers. Thus, it is believed that DR can be used to support the construction of a management model for people with diabetes in the context of Primary Health Care, as a strategy for the prevention and control of future complications, as pointed out in

previous studies (SIMÓ-SERVAT; HERNÁNDEZ; SIMÓ, 2019; JENKINS *et al.*, 2015; VUJOSEVIC; SIMÓ, 2017). It is also highlighted the need to build and improve more accessible resources in order to track the presence of biomarkers related to risk factors for micro vascular complications, using DR as a reference biomarker (SIMÓ-SERVAT; HERNÁNDEZ; SIMÓ, 2019; JENKINS *et al.*, 2015; VUJOSEVIC; SIMÓ, 2017). Therefore, we propose to investigate in the literature the biomarkers that indicate morbidity in people with DR. This study, therefore, aimed to identify morbidity biomarkers in people with DR.

METHODS

This is an integrative literature review based on studies that investigate the biomarkers of morbidity in people with DR. The integrative review consists of combining data from different study designs, enabling a holistic comprehension of the topic under study, while describing the state of science and supporting the development of theories. For this reason, this possibility of methodological combinations plays a relevant role in evidence-based nursing practices (HOPIA; LATVALA; LIIMATAINEN, 2016). Full studies published between 2010 and November 2020 related to morbidity biomarkers in people with diabetic retinopathy were included. The search was performed in databases referring to the area of health sciences, such as: BVS, PubMed and Scielo. As search strategy, terms indexed in DeCS and MeSH were used: Morbidity; biomarkers; diabetic retinopathy. The descriptors were searched in the English language and the Boolean term used was AND. It also consisted of selecting the text availability filters, selecting the complete ones, the language for English, Spanish and Portuguese, restriction of the publication period between 2010 and 2020 and the types of studies included were observational, comparative and multicentric. The search for studies proceeded in two stages: initially without establishing filters and later, selecting the aforementioned filters (Chart 1). The strategy was based on the PECOS system, characterized as Population, Exposure, Comparator, Outcome and Types of studies, with the population being composed of people with diabetes mellitus; exposure related to diabetic retinopathy; the comparators were the biomarkers; the outcome, related to morbidity; and regarding the types of studies, observational, comparative and multicenter studies were included.

Chart 1. Search result distributed by the combination of descriptors and search code before and after filters

Descriptors	PUBMED	BVS	SCIELO
Morbidity and biomarkers and diabetic retinopathy	306	228	0
Duplicate	226		
Descriptors with filters	PUBMED	BVS	SCIELO
Morbidity and biomarkers and diabetic retinopathy	44	76	0

Source: Survey data, 2020.

The selection of studies was conducted by the author, independently, who initially chose the references in the databases utilized. Then, one of the researchers selected the publications eligible for review, by reading their titles, abstracts and later the full text. After reading, the ordering and analysis of the articles was conducted, considering the study authors, year of publication, study site, type of study, objectives and morbidity biomarkers identified in people with diabetic retinopathy. The main results found were synthesized in text and chart, which consisted of the ordering of authors and publication date, type of study, study site, objectives, identified biomarkers and outcomes.

RESULTS

After identifying and evaluating the 120 articles found in the databases, using filters, only six corresponded to the objective of this study. As for the origin of the articles, four are from the Asian continent, two from China, one from India and one from Japan, and two articles are from the European continent and originated in Spain

and Denmark. Five of these are observational type and only one multicentric. The biomarkers that indicated morbidity in people with diabetic retinopathy in the study findings were diverse, including: serum triglycerides, neutrophil-lymphocyte ratio (NLR) and ankle-brachial pulse wave velocity (baPWV), proliferative diabetic retinopathy associated with proteinuria, retinal arteriolar narrowing, inferior retinal fractal dimension, coronary artery calcium score (CACS) >400, coronary stenosis >50%, association of glycated hemoglobin levels (HbA1c) >7% with individuals with diabetes duration >10 years, and urinary haptoglobin. Despite the diversity of biomarkers, it was found that the outcomes of the studies were similar, with four referring to macrovascular complications of diabetes (cardiovascular events and atherosclerosis) and two outcomes concerning microvascular complications (kidney disease/nephropathy and neuropathy) (Chart 2).

DISCUSSION

The analyzed studies address the biomarkers present in people with DR predictive of micro and macrovascular complications due to DM. Despite the use of intensive statin therapy in people with hypercholesterolemia and diabetic retinopathy, without a history of cardiovascular disease (CVD), there was no reduction in lipid levels (TADA *et al.*, 2018). Thus, it was observed that intensive statin therapy was not superior to standard therapy for reducing cardiovascular events. In addition, serum triglycerides have shown to be strongly associated with early cardiovascular events in people with diabetic retinopathy. It was also found a significantly increased risk of CVDs in people with diabetes and high levels of triglycerides (TGs) even after statin therapy (NICHOLS *et al.*, 2019). The study reveals that despite the high proportion of people with diabetes who maintain high levels of TGs, research on the association between this biomarker and CVDs is still scarce. Accordingly, they suggest that other studies investigate the efficacy of new drugs that reduce serum TG levels in individuals who have high-risk diabetes accompanied by hypercholesterolemia and diabetic retinopathy, focusing on lipoproteins, which are rich in TGs and their control can be an important contributor to reduce cardiovascular events (TADA *et al.*, 2018). It was identified the association of the neutrophil-lymphocyte ratio (NLR) with the ankle-brachial pulse wave velocity (baPWV) in patients with DR and both were found to be elevated both in type 2 diabetes and in the presence of DR (WANG *et al.*, 2015). This association indicates a close relationship between the inflammatory processes caused by neutrophils and the consequent arterial stiffness. For this reason, the authors suggest that NLR can be widely used as a biomarker for early detection of undiagnosed subclinical atherosclerosis in patients with DM2 and DR, as it is a low-cost, accessible test for evaluation and is part of routine laboratory tests. Added to this, the importance of early assessment of baPWV, which is also an indicator of atherosclerotic abnormalities. Corroborating these findings, the meta-analysis study (LUO; ZHANG, 2019), identified that the NLR was found to be considerably increased in people with DR when compared to those with DM without retinopathy, which suggests an agreement with the research data (WANG *et al.*, 2015) in reference to the use of NLR as a biomarker of morbidity present in DR. However, the authors emphasize that, due to the reduced number of articles available for meta-analysis, identified only four that address the correlation between neutrophil-lymphocyte ratio and the severity of diabetic retinopathy, it is necessary to develop more studies research to elucidate this association. In order to assess DR as a long-term marker of all-cause mortality in type 1 diabetes, it was found that the mortality rate in people with proliferative diabetic retinopathy (PDR) was higher when compared to people without DR or with non-proliferative diabetic retinopathy (NPDR) (GRAUSLUND, 2011).

Chart 2. Summary of the main results found

Author & Publication Date	Kind of study	Study Location	Goal	Biomarkers identified	Outcomes
Tada <i>et al.</i> (2018)	Multicenter study	Japan	Test whether serum triglycerides are associated with early cardiovascular events in diabetic patients	Serumtriglycerides	Cardiovascular events
Wang <i>et al.</i> (2015)	Observational study	China	To investigate the association of neutrophil-lymphocyte ratio (NLR) with ankle-brachial pulse wave velocity (baPWV) in patients with DR.	Neutrophil-lymphocyte ratio (NLR) and ankle-brachial pulse wave velocity (baPWV)	Atherosclerosis
Grauslund (2011)	Observational study	Denmark	Evaluate diabetic retinopathy as a long-term marker of all-cause mortality from type 1 diabetes mortality and use retinal vascular analyzes to investigate the associations of long-term micro- and macrovascular complications and retinal vascular diameters and retinal fractal in type 1 diabetes.	Proliferative diabetic retinopathy associated with proteinuria; Arteriolar retinalnarrowing; Lowerretinal fractal dimension	All-cause mortality in DM1; Nephropathy and macrovascular disease; Neuropathy.
Simó <i>et al.</i> (2019)	Observational study	Spain	To examine whether evaluation of diabetic retinopathy is useful to identify patients at increased risk for silent subclinical cardiovascular disease.	Coronary Artery Calcium Score (CACs) >400; Coronarystenosis	Subclinical Cardiovascular disease
Pradeepa <i>et al.</i> (2015)	Observational study	India	Evaluate the relationship between diabetic retinopathy and coronary artery disease in Asian Indians	Glycated hemoglobin (HbA1c) levels >7% and individuals with diabetes duration >10 years	CoronaryArteryDisease
Yang <i>et al.</i> (2016)	Observational study	China	Check whether a proteome of urine specific for vision-threatening proliferative diabetic retinopathy is an indicator to predict chronic renal failure in patients with DM2.	Urinaryhaptoglobin	Kidney disease in people with DM2

Source: Survey data, 2020

By associating PDR with proteinuria, it was noticed that both are the greatest predictors of mortality in DM1. In evaluating the relationship between retinal arteriolar caliber and micro- and macrovascular complications, it was suggested that fundus retinal photographs could be used to track the risk of non-ophthalmic complications in DM1, as patients with arteriolar retinal narrowing are 2.17 and 3.17 times more susceptible to developing nephropathy and macrovascular diseases, respectively (GRAUSLUND, 2011). Furthermore, it was highlighted that lower fractal dimensions lead patients to greater risks of developing PDR and neuropathy. In accordance with these data, it was highlighted that PDR is twice as related to mortality from CVD, acting as an important predictor of this risk when compared to light or non-proliferative DR. Therefore, the authors suggest the importance of early diagnosis and treatment of DR aiming to reduce the risk of death for patients (XU *et al.*, 2020). The inferior fractal vascular dimension of the retina had constant associations with the incidence of the three microvascular complications in DM1 (proliferative diabetic retinopathy, peripheral neuropathy and nephropathy) over 16 years (BROE *et al.*, 2014). This indicates that the retinal vascular fractal dimension is a possible common biomarker of the three morbidities, as well as the progression of DR to the more severe forms.

It was realized, therefore, that retinal vascular imaging is a non-invasive diagnostic tool, useful to detect the severity and progression of retinopathy, and consequent early risk stratification of micro and macrovascular complications (GRAUSLUND 2011; BROE *ET AL.* 2014; KEE; WONG; LI, 2017). Carotid artery calcium scores (CACs) were shown to be high in patients with DM2 (CACs >400) and they also had a high rate of coronary stenosis (>50% in at least one coronary artery). The association between the degree of DR and the presence of coronary stenosis was also evidenced, whose moderate-severe DR indicates a higher prevalence of subclinical CVDs compared to slight or absent DR (SIMÓ *et al.*, 2019). Therefore, the authors suggest that moderate-severe DR is a potent predictor of CVD risk. For this reason, they recommend early identification of CACs as well as the rate of coronary stenosis to identify and control the risk of people with type 2 diabetes for developing cardiovascular disease, based on unconventional biomarkers. It is noteworthy that people with PDR have a higher risk of mortality from CVDs, however, there are few studies that address the association of light or absent DR as a predictor of these morbidities. Thus, the authors suggest monitoring people with NPDR, considering that they have a high potential to develop the most severe form of the disease (XU *et al.*, 2020). It was noticed once again, conformity towards the relationship of diabetic retinopathy with coronary artery disease (CAD) (PRADEEPA *et al.*, 2015), in which a high prevalence of CAD was observed in Asian Indians with higher degrees of DR, that is, those with severe NPDR and PDR had a marked prevalence of CAD. In addition, a significant association of DR with CAD was noticeable in individuals who had HbA1c levels >7% and diabetes duration >10 years. In view of the association, they found that individuals with type 2 diabetes retinopathy had twice the risk of incident coronary artery disease and three times the risk of death from CAD, even without having common characteristics for the development of the disease, such as blood glucose levels high, cardiovascular risk factors and large vessel atherosclerosis (CHEUNG *et al.*, 2007).

Taking into account the findings in the studies Grauslund (2011), Xu *et al.* (2020), Simó *et al.* (2019), Pradeepa *et al.* (2015) e Cheung *et al.* (2007), there is agreement between the authors regarding the fact that microvascular disease, as a result of DR, significantly contributes to the risk of coronary artery disease and cardiovascular events. Thus, the authors emphasize that diabetic retinopathy can be a reference biomarker for tracing micro- and macrovascular complications in people with diabetes. In a complementary way, it was indicated that DR is also identified as a clinical biomarker for the diagnosis of diabetic kidney disease (DKD), through the results of a study, which identified that patients with reduced renal function had PDR (YANG *et al.*, 2016). The study, therefore, suggests that urinary haptoglobin, specific for proliferative diabetic retinopathy, has been shown to be more reliable for predicting early decline in kidney function in people

with DM2. The study by Zhang *et al.* (2018) highlights, similarly to Yang *et al.* (2016), that the existence of diabetic retinopathy may indicate determinants that predispose the individual to an increased risk of developing diabetic nephropathy (DN) or severe kidney damage, both resulting from damage to the microvasculature. Added to this, it is confirmed that urinary haptoglobin predicted the progression of kidney disease and substantially improved the predictive performance of albuminuria in order to track the decline in renal function in Asians with DM2 (LIU *et al.*, 2016). Once again, the close relationship between the presence of DR and the risk of microvascular (diabetic peripheral neuropathy and nephropathy) and macrovascular (acute myocardial infarction and stroke) complications is observed. Thus, studies highlight the importance of early identification of biomarkers predictors of morbidity associated with diabetic retinopathy (KEE; WONG; LI, 2017; XU *et al.*, 2020; CHEUNG *et al.*, 2007).

FINAL CONSIDERATIONS

The studies addressed the different types of biomarkers that represent the risk of morbidity present in people with diabetic retinopathy. Furthermore, it was also found that the identified biomarkers caused similar outcomes, such as microvascular complications (kidney disease/nephropathy and neuropathy) and macrovascular complications (cardiovascular events and atherosclerosis) of diabetes. These outcomes represent the causes/determinants of morbidity in people with diabetes affected by diabetic retinopathy. In this regard, from the identification of the risk biomarkers of complications associated with DR, it was possible to confirm, based on the scientific literature, that the damage caused to the retinal microvasculature and its progression lead to the development of DM complications, which can be tracked through predictive morbidity biomarkers. Thus, the present study suggests that people with diabetes who have DR should be more specifically evaluated and managed within the scope of Primary Health Care, through the screening and control of morbidity biomarkers based on the presence of DR, aiming to reduce the high levels indicators of morbidity and mortality from diabetes.

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