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Review Article

Emotional Status and Quality of Life in Patients with Diabetic Retinopathy: A Review

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Abstract

Purpose of review: This review paper aims at discussing the association of Diabetic Retinopathy (DR) with vision-related quality of life and emotional status of patients, as well as the potential association between the disease's severity, emotional disturbances and the manifestation of anxiety, depression and psychological features. Future directions are suggested. **Recent findings:** Diabetic Retinopathy represents a major and detrimental consequence of Diabetes Mellitus (DM). The presence of DR and especially progressed stages of the disease, negatively impacts patients' quality of life and emotional status. Unsurprisingly, patients potentially have to deal with psychological disturbances, like anxiety and depressive manifestation, in the context of emotional imbalance, adding an additional burden to patients' well-being. Advanced stages of DR, mostly Severe Non-Proliferative Diabetic Retinopathy (NPDR) or Proliferative Diabetic Retinopathy (PDR), are, in general, associated with heavier disease and more severe visual impermanent heightening the risk of subsequent emotional disturbances. **Summary:** Diabetic Retinopathy and especially advanced stages of the disease can affect a wide array of aspects that define patient's quality of life and emotional status. A bi-directional correlation between DR progression and emotional manifestations is coming at the forefront of interest, underscoring the significance of unveiling and dealing with the emotional constituents of the disease in order to halt DR worsening. A timely diagnosis with fundoscopy and subsequent measure for DR stabilization, through vision improvement can positively affect the emotional and functional well-being of patients in the long run.

Keywords: Evaluation of life in diabetes; Emotional disturbances in Diabetic Retinopathy; Emotional status in Diabetic Retinopathy; Anxiety and depression in Diabetic Retinopathy; Visual related quality of life in Diabetic Retinopathy

Introduction

Diabetic Retinopathy

Diabetes Mellitus represents one of the major public health issues worldwide. In the United States almost 23 million people have been diagnosed with diabetes, it is estimated that 7 more million people suffer undiagnosed. DM constitutes a chronic, multisystemic, metabolic disease with increased glucose serum levels being the characteristic finding [1,2]. Diabetes type 1 and type 2 represent the most prevalent forms of the disease. In type 1 pathogenesis is caused by beta cell destruction. Type 2 is characterized by a combination of both insulin resistance and impaired beta cell function [1]. The two forms share in the common the increased glucose levels [3]. DM can impact many organs, mainly the kidneys, heart, and central nervous system. Ophthalmic manifestations, with Diabetic Retinopathy (DR) representing

the major morbidity, are among the most severe complications [1]. Vascular Endothelial Growth Factor (VEGF) represents the most significant angiogenetic factor in the development of DR [1,4]. The main clinical separation of DR is between two forms, based on the disease's severity and the presence or absence of abnormal retinal neovascularization, i.e., Non-Proliferative DR and Proliferative DR [4,5]. A wide array of visual complications in DR can lead to severe visual deterioration, including, diabetic macular edema (DME) secondary to capillary leakage, macular ischemia and diabetic papillopathy caused by capillary occlusion, and hemorrhages, tractional retinal detachment, and neovascular glaucoma, whether disease progresses to the proliferative form [1,6]. The incidence of DR associated with chronicity of the disease and aging, is increased irrespective of DR type. A seminal study in the field, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that after 20 years of DR, the vast majority of patients, almost 99% of Type 1 and 60% of Type 2 patients, would have some degree of ocular disease. Regarding the potential risk a decade after the initial diagnosis of diabetes, the vast majority of patients with Type 1, and nearly 67% with Type 2, are expected to have DR manifestations of varying severity [1].

Quality of Life and Emotional Status in Patients with Diabetic Retinopathy

Diabetic Retinopathy and especially the advanced stages of the disease, can significantly impair patients' quality of life and emotional status. DR can lead to visual deterioration, impacting patients' daily life and adding up to the disease burden. In addition, visual decline has been associated with deterioration in a series of indexes important for patient's well-being such as social isolation, dependency in daily life and withdrawal from physical activity [7]. The aforementioned reality can result in emotional discomfort and manifestations from the psychological sphere rendering patients vulnerable to anxiety disturbances and even depressive symptomatology. If that the case, the general health status of patients becomes more challenging and difficult [1,8]. Among the potential feelings that DR could have to deal with, are desperation and sadness, and fear for further future visual deterioration and sadness. It is worth noting that significant percentage of those patients face daily life challenges secondary difficulties in social relationships, working environment, self-sufficiency, as well as commuting issues due to restrictions on driving and usage of public transport. Findings have shown, that even patients with minor DR manifestations feel unsafe vision-wise [9].

In order to evaluate the suggested impact of DR on patients' quality of life, utilizing specifically designed questionnaires for this purpose can be can be significantly helpful. Central role has the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), a crucial tool in the evaluation of Vision-Related Quality of Life (VR-QOL), meeting the prerequisites for a questionnaire of its kind, that is, evaluation of a series of qualitative features, such self-efficiency, visually-depended daily activities, emotional well-being and socializing. Furthermore, it is in in line with the 3 components defined by the World Health Organization's International Classification of Functioning Disability and Health (WHO-ICF) for evaluating health-related implications of a disease: impairment, activity limitations, and participation restriction. Patients self-reported feedback is utilized to qualitatively and quantitatively estimate the burden the disease of interest [1,10]. Besides DR, NEI-VFQ has been utilized in measurement VR-QOL in a variety of eye diseases, such as age-related macular degeneration and glaucoma. The common denominator is the constant finding that visual acuity affects the VR-QOL mainly in role-achieving endeavors, as well as near and distance activities [11]. Furthermore, another instrument in our armamentarium is the Beck Anxiety Inventory (BAI), a psychometric rating scale utilized to measure the severity of anxiety. BAI is considered a reliable screening tool for anxiety as an effective way of discrimination between anxious and non-anxious individuals [1].

The psychological impact of DR is emerging as a major constituent of the disease. Given the limited information provided in the literature regarding evidence-based approach regarding the degree of social and emotional impact of DR and the subsequent necessity of psychological support to the sufferers, in 2023 Saitakis et al assessed the quality of life in patients with DR or DR including diabetic macular edema. The authors also investigated the potential association between the disease's severity, emotional status of patients, and the manifestation of anxiety and psychological disorders, utilizing the BAI and VFQ scales [1] (Tables 1 and 2).

		B +	SE ++	*p*
General Health				
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.201	0.144	0.166
	Moderate Non-Proliferative Diabetic Retinopathy	−0.315	0.157	**0.047**
	Severe Non-Proliferative Diabetic Retinopathy	−0.376	0.159	**0.019**
	Proliferative Diabetic Retinopathy	−0.712	0.127	**<0.001**
Time spending sitting per day (hours)		−0.051	0.014	**<0.001**
General Vision				
Educational level	College/University/MSc (reference)			
	Primary school at most	−0.120	0.048	**0.014**
	Middle/High school	−0.057	0.047	0.228
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.014	0.057	0.801
	Moderate Non-Proliferative Diabetic Retinopathy	−0.029	0.063	0.648
	Severe Non-Proliferative Diabetic Retinopathy	−0.043	0.065	0.51
	Proliferative Diabetic Retinopathy	−0.255	0.055	**<0.001**
Time spending sitting per day (hours)		−0.020	0.006	**0.001**
Beck Anxiety Score		−0.004	0.001	**0.002**
Ocular Pain				
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.084	0.073	0.253
	Moderate Non-Proliferative Diabetic Retinopathy	−0.050	0.08	0.53
	Severe Non-Proliferative Diabetic Retinopathy	−0.018	0.082	0.823
	Proliferative Diabetic Retinopathy	−0.270	0.066	**<0.001**
Beck Anxiety Score		−0.007	0.001	**<0.001**
Near Activities				
Employed	No (reference)			
	Yes	0.147	0.053	**0.007**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.086	0.078	0.27
	Moderate Non-Proliferative Diabetic Retinopathy	−0.039	0.086	0.65
	Severe Non-Proliferative Diabetic Retinopathy	−0.026	0.088	0.769
	Proliferative Diabetic Retinopathy	−0.318	0.071	**<0.001**
Beck Anxiety Score		−0.003	0.002	**0.05**
Distance Activities				
Employed	No (reference)			
	Yes	0.156	0.055	**0.006**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.080	0.081	0.323

	Moderate Non-Proliferative Diabetic Retinopathy	−0.155	0.088	0.083
	Severe Non-Proliferative Diabetic Retinopathy	−0.032	0.091	0.729
	Proliferative Diabetic Retinopathy	−0.361	0.075	**<0.001**
Time spending sitting per day (hours)		−0.016	0.008	**0.047**
Beck Anxiety Score		−0.005	0.002	**0.002**
Social Functioning				
Employed	No (reference)			
	Yes	0.093	0.043	**0.032**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.045	0.062	0.472
	Moderate Non-Proliferative Diabetic Retinopathy	−0.023	0.069	0.741
	Severe Non-Proliferative Diabetic Retinopathy	0.02	0.07	0.779
	Proliferative Diabetic Retinopathy	−0.290	0.057	**<0.001**
Time spending sitting per day (hours)		−0.027	0.006	**<0.001**
Beck Anxiety Score		−0.003	0.001	**0.007**
		β+	**SE++**	***p***
Mental Health				
Employed	No (reference)			
	Yes	0.144	0.055	**0.009**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.124	0.079	0.121
	Moderate Non-Proliferative Diabetic Retinopathy	−0.028	0.087	0.75
	Severe Non-Proliferative Diabetic Retinopathy	0.017	0.09	0.852
	Proliferative Diabetic Retinopathy	−0.357	0.074	**<0.001**
Time spending sitting per day (hours)		−0.029	0.008	**0.001**
Beck Anxiety Score		−0.010	0.002	**<0.001**
Role Difficulties				
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.072	0.119	0.548
	Moderate Non-Proliferative Diabetic Retinopathy	−0.007	0.131	0.958
	Severe Non-Proliferative Diabetic Retinopathy	−0.060	0.133	0.655
	Proliferative Diabetic Retinopathy	−0.463	0.108	**<0.001**
Beck Anxiety Score		−0.010	0.002	**<0.001**
Dependency				
Employed	No (reference)			
	Yes	0.165	0.076	**0.031**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.136	0.111	0.222
	Moderate Non-Proliferative Diabetic Retinopathy	0.018	0.121	0.879
	Severe Non-Proliferative Diabetic Retinopathy	−0.012	0.124	0.923

	Proliferative Diabetic Retinopathy	−0.454	0.101	**<0.001**
Beck Anxiety Score		−0.012	0.002	**<0.001**
Driving				
Age		−0.005	0.002	**0.03**
Color Vision				
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.024	0.074	0.744
	Moderate Non-Proliferative Diabetic Retinopathy	−0.022	0.081	0.782
	Severe Non-Proliferative Diabetic Retinopathy	−0.082	0.081	0.308
	Proliferative Diabetic Retinopathy	−0.366	0.063	**<0.001**
Peripheral Vision				
Employed	No (reference)			
	Yes	0.111	0.049	**0.024**
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.046	0.071	0.516
	Moderate Non-Proliferative Diabetic Retinopathy	−0.017	0.08	0.834
	Severe Non-Proliferative Diabetic Retinopathy	−0.053	0.08	0.505
	Proliferative Diabetic Retinopathy	−0.306	0.065	**<0.001**
Beck Anxiety Score		−0.005	0.001	**<0.001**
Composite VFQ-25 score				
Educational level	College/University/MSc (reference)			
	Primary school at most	−0.119	0.042	**0.005**
	Middle/High school	−0.060	0.041	0.151
Fundoscopy	Without findings (reference)			
	Mild Non-Proliferative Diabetic Retinopathy	−0.042	0.05	0.4
	Moderate Non-Proliferative Diabetic Retinopathy	−0.023	0.055	0.679
	Severe Non-Proliferative Diabetic Retinopathy	−0.006	0.057	0.92
	Proliferative Diabetic Retinopathy	−0.247	0.048	**<0.001**
Time spending sitting per day (hours)		−0.022	0.005	**<0.001**
Beck Anxiety Score		−0.005	0.001	**<0.001**
Note: Logarithmic transformations were used in these analyses. + regression coefficient ++ Standard Error.				

Table 1: Multivariate regression analyses results with scores in VFQ-25 subscales as dependent variables.

	Beck Anxiety Score		
Gender	**Mean (SD)**	**Median (IQR)**	**p Mann–Whitney Test**
Men	24.5 (18.8)	24.5 (10–36)	0.611
Women	22.4 (16.7)	21.5 (7.5–33.5)	
Age, r ‡	−0.09		0.297
Married/Living with partner			
No	24.4 (18.3)	22 (11–36.5)	0.701
Yes	22.7 (17.4)	22.5 (6–33)	
Educational level			
Primary school at most	23.6 (19)	21 (8–37)	0.982+
Middle/High school	22.8 (17.8)	25 (4.5–35)	
College/University/MSc	23.6 (16.3)	24 (12–34)	
Employed			
No	24.3 (19.1)	22 (8–36)	0.631
Yes	21.9 (15.3)	23 (9–32)	
Smoking habits			
Smokers	25.1 (20.2)	26 (10–39)	0.827+
Nonsmokers	23.2 (17.1)	21 (9–34.5)	
Ex-smokers	22 (17.4)	23 (8–30)	
Alcohol consumption			
No	23.7 (18)	23 (9–36)	0.789
Yes	22.6 (16.5)	23.5 (10–30)	
Physically active			
No	24.6 (18.4)	25 (10–36)	0.21
Yes	19.6 (15.1)	20.5 (6–31)	
Time spending sitting per day (hours), r ‡	0.23		0.007
Years with diabetes, mean (SD)	0.29		0.001
Type of diabetes			
Type 1	25.9 (17.1)	25 (15–34)	0.199
Type 2	21.8 (17.9)	21 (5–34)	
Treatment with pills only or combined with something else			
Pills only	25.6 (16.4)	25 (14.5–35.5)	0.132
Combined	21.5 (18.5)	19.5 (2–34)	
Treatment with insulin only or combined with something else			

Insulin only	17.9 (17.5)	14 (0–32)	0.002
Combined	27.1 (16.9)	25 (15–39.5)	
Concomitant disease			
No	16 (13.4)	15 (0–23)	0.029
Yes	24.7 (18.1)	25 (9.5–36)	
Fundoscopy			
Without findings	16.1 (13.2)	15.5 (2–26)	0.002
With findings	26.6 (18.5)	26.5 (11–39)	
Fundoscopy			
● Without findings	16.1 (13.2)	15.5 (2–26)	**0.001** +
Mild Non-Proliferative Diabetic Retinopathy	17.5 (16.1)	18 (0–32)	
Moderate Non-Proliferative Diabetic Retinopathy	24.1 (14.5)	23 (14–32)	
● Severe Non-Proliferative Diabetic Retinopathy	29.6 (15.4)	31.5 (25–36)	
● Proliferative Diabetic Retinopathy	31.7 (21.0)	30 (14–50)	
Diabetic Macular Edema			
No	19.9 (16.1)	20.5 (5.5–30)	0.001
Yes	30.4 (18.9)	32.5 (16–45)	
Treatment with anti-VEFG injections			
No	20.5 (16)	21 (6–30)	0.002
Yes	32.3 (20)	34 (16–49)	
Number of doses, r ‡	−0.42		0.015

Kruskal–Wallis test; ‡ Spearman's correlation coefficient; ● Clinically significant differences between (1) without findings—Severe Non-Proliferative Diabetic Retinopathy and (2) without findings Proliferative Diabetic Retinopathy.

Table 2: Association of BAI score with patients' characteristics.

Severity of Diabetic Retinopathy and Emotional Impact

Severe Non-Proliferative Diabetic Retinopathy or Proliferative Diabetic Retinopathy, represent the advanced stages of DR, are associated with more severe disease and visual deterioration, increasing the risk of subsequent emotional disturbances.

Recently, Saitakis et al demonstrated that patients with fundoscopic findings had significantly lower scores in all VFQ-25 subscales compared to patients without, indicating deteriorating quality of life for DR patients. The study demonstrated that a series of constituents, that is, DR severity, greater levels of anxiety, daily sitting time, unemployment and lower education level were found to be significantly, negatively associated with a worse quality of life. More specifically, patients with Moderate Non-Proliferative Diabetic Retinopathy, Severe Non-Proliferative Diabetic Retinopathy or Proliferative Diabetic Retinopathy had significantly worse general health compared to patients without findings in their fundoscopy [1]. Another recent cross-sectional study assessed the effect of DR on VR-QOL in patients with type 2 diabetes. The severity of DR in the eyes was divided into 5 grades: no DR, mild non-proliferative diabetic retinopathy, moderate NPDR, severe NPDR, and proliferative diabetic retinopathy. Severity scores from both eyes were then summarized to create a single per-person grade ranging from 1 (no DR in either eye) to 7 (bilateral PDR). Among the 1537 participants 54.4% had no DR, 31.2% mild NPDR, 5.9% moderate NPDR, 4.7% severe NPDR and 3.9% PDR. The study evaluated the impact of DR severity. As disease progresses, lower scores were shown on a series of qualitative aspects, such as role-sufficiency general vision, near and distance activities, socializing, self-efficiency, mental health, general, color and peripheral vision. Regarding the role constituent, there were two remarkable thresholds of disease severity, transition

a) from bilateral mild NPDR to mild NPDR/>mild NPDR and b) from moderate NPDR/≥moderate NPDR to severe NPDR/≥severe NPDR [12].

Presence of Proliferative Diabetic Retinopathy seems to come with a heavier burden in many aspects including the general quality of life. Patients with PDR experience significantly greater anxiety levels and have significantly worse general health and vision, when compared with patients without retinal lesions. The suggested interpretation, is that the advanced nature of the disease is usually accompanied by a general health decline, thus enhancing anxiety manifestations. In addition, this subgroup, not surprisingly, endorses more ocular pain and discomfort [1]. PDR may lead to neovascular glaucoma, a condition associated with severe pain, increased eye dryness and worse visual potential, resulting in further decline in patient's daily life, not only emotionally, but also functionally [6,13]. Proliferative disease was also found to be associated with worse visual performance, both for near and far activities, and impaired color and peripheral vision as well. This may further withdraw patients from involving in their daily life activities, thus sparking anxiety. Findings show also that patients with PDR had lower scored regarding social functioning, mental health, role adequacy and dependency indices. Even therapeutic measures in PDR treatment can contribute to increased discomfort or pain. The Panretinal Photocoagulation (PRP) is a mainstay approach in patients with PDR to coagulate ischemic retinal and deal with neovascularization. The therapy itself can also cause ocular discomfort, as well as leading to accommodation impermeant [1]. On the other hand, PDR not affecting vision, due to traction on the macula or vitreous hemorrhage, may often be asymptomatic. Moreover, it has been suggested that patients with severe long-standing PDR may have adapted to the changes in their visual status [14].

Visual Acuity in Patients with Diabetic Retinopathy and Quality of Life

Visual acuity is a crucial constituent of quality of life in patients with DR. A study in India confirmed this association. It showed that the aspects mostly affected were distance and near activities. In addition, aging and comorbidities found to be associated with poorer QOL in DR patients [3]. Furthermore, an Italian study evaluated vision-related quality of life in patients with visual acuity <5/10 in the better eye induced by retinopathy using the NEI VFQ-25. Worse visual acuity corresponded to lower scores in wide spectrum of indexes, including near and distance activities, general, color and peripheral vision, visual-specific social involvement, self-efficiency, role-completion, driving and mental health [15]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy had investigated changes of vision-related quality of life during a 10-year period in a type 1 diabetes population. It was shown that the threshold of visual impairment associated with negative changes in the NEI-VFQ-25 scores was the loss of three lines in the better eye in the ETDRS chart. Interestingly, the impairment in patient's functionality was noted not only in aspects directly related to visual performance (near and distance activities), but also in additional qualitatively constituents, mainly driving, daily life roles, mental health and self-efficiency. In addition, unemployment and the presence of systemic comorbidities such as nephropathy were significantly associated with decline in VR-QOL indexes. In contrast, DR progression was not shown to have an impact 10 years after the initial diagnosis. In this time period of 10 years, only 7 people developed DME in their better seeing eye [14].

Diabetic Retinopathy and Anxiety

Anxiety represents a clinical entity, featuring alertness and feelings of fear, tension and anxiety in daily life. It is the most frequent represents the most frequently encountered mental disorder in Europe. Anxiety disorders have an annual prevalence of 14% at the ages of 14-65 and the entity has a predilection to manifest in women [16]. Regarding the prevalence of anxiety in adults with diabetes, a systematic review of the literature showed that generalized anxiety disorder manifests in 14%. Crucial impact is the prevalence of anxiety symptomatology in patients with diabetes who take part in clinical studies with the estimated percentage rising up to 40% [1]. In this context, anxiety can add an additional burden for patients have DR findings in fundoscopy.

It has been suggested that Anxiety and DR may show interconnection with a potential association between the disease's severity, emotional status of patients and the subsequent manifestation of anxiety and psychological disturbances. Moreover, it has been strongly suggested that the presence of Anxiety could contribute to further progression of DR. Saitakis et al showed that greater anxiety symptoms were significantly associated with worse quality of life in all domains except for general health, driving and color vision. Unsurprisingly, presence of Anxiety is associated with a deterioration not only in patient's physical power, but also in emotional reserves, thus undermining the ability of patients to complete daily life endeavors compared to patients with DR of the same severity, but without anxiety [1]. In addition, it should be underscored that visual performance has a non-organic, functional constituent, which depends on the psychological status. Patients suffering from anxiety could face low self-esteem and self-confidence, features rendering them even more vulnerable, as they tend to underestimate their visual potential and the ability to correspond under emotional pressure [1,16]. The study also showed that the presence of concomitant diseases, was also associated with significantly greater anxiety. Additional comorbidities in individuals with DR seem to further deteriorate the emotional status of patients [1].

Regarding fundoscopy, the research work demonstrated higher levels of anxiety in those with retinal findings. Furthermore, it is well-established that DME is the prominent cause of visual loss in DR patients and its presence in general means deteriorated vision. Indeed, the study showed that the presence of DME was associated with higher levels of anxiety. The impact of anti-VEGF treatment on patients' emotional status was also evaluated. It was demonstrated that not only treatment with anti-VEFG injections,

but also an increased number of doses of anti-VEFG injections were also significantly correlated with greater anxiety levels. The suggested interpretation is that the thought of receiving an intraocular injection, especially when frequently performed, may scare patients. In addition, an injection itself in the eye may often be accompanied by a certain amount of pain, discomfort, redness or hyposphagma. Regarding emotional status, more years of disease, treatment with insulin and the hours being idle per day were all correlated with greater anxiety. Multivariate analysis showed that presence of Severe-NDPR or PDR in fundoscopy, as well as receiving insulin (alone or in combination with another treatment), were significantly correlated with an increased burden of anxiety [1].

A recent study evaluated the potential association between DR, disease severity and the manifestation of anxiety and depression. It was shown that only PDR presence was associated with increased risk of a subsequent diagnosis of anxiety. Especially, in the demographic 18-34-year-old, patients with either NPDR or PDR had increased chances of manifesting anxiety or depression. The study also demonstrated that the odds of emotional disorders to occur, increase as disease progresses to the proliferative form. They commented that the aforementioned finding coincides with an elevated anxiety prevalence within this age group. Interestingly, when stratified for age and sex, it was shown that NPDR did not increase the risk of subsequent anxiety disorder. Surprisingly, PDR was found to reduce the probability of future anxiety diagnosis in older age. This finding was attributed to an alleged protective effect against anxiety manifestation seen in all older age groups [17].

A potentially Bi-Directional Relationship between Diabetic Retinopathy and Anxiety

A crucial bi-directional association may exist among patients with Diabetic Retinopathy and coexistent or developing psychological disorders. It is well known that increased levels of circulating cytokines have been observed both in patients with diabetes and psychiatric disorders. It is suggested that the coexistence high cytokines levels and insulin deficiency may lead to neurocognitive deficits, inappropriate neural development and serum glucose fluctuations [18,19]. The hypothesis involves the Hypothalamic-Pituitary-Adrenal (HPA) pathway. A dysregulation in HPA could cause hypercortisolemia and subsequently to alterations in insulin resistance, thus leading to DR manifestation [1]. Diabetes seems to have dual features, representing both an upstream event for stress, and simultaneously being a disease that could emerge from chronic stressful context. Indeed, a series of epidemiological studies have shown that diabetes is a common stress-driven disease and stressful life events heighten the risk of diabetes occurrence. A potential mechanism correlating stress and insulin evolves molecular pathways, including pancreatic beta cells, lipid metabolism, the renin-angiotensin system, the autonomic nervous system, the immune response system and endocrine hormones which fluctuate depending of stress [20]. The realization that underlying psychological disorders, like anxiety and depression, may be a major contributing factor to the progression of DR, is crucial in understanding the significance of a multidisciplinary approach to dealing with diabetes and its repercussions [17].

Diabetic Retinopathy and Depression

Depression represents a major public health issue globally with an increasing prevalence. Patients with diabetes have almost double risk of manifesting depression in their lifetime. Regarding visual function and depression, it seems to be an association between visual deterioration and depressive symptomatology. When DM and visual decline coexist, patients may be even more susceptible to manifest depression. In addition, certain socioeconomic and demographic characteristics are linked with an increased risk of depression in patients with DM, including not being married, a lower income, gender, social status, blood glucose level, insulin treatment, as well as lower level of education [9,11]. Studies have shown that 1-unit (%) increase in HbA1c was associated with a 2-point increase in depression score, as well as a higher depression rate for males with a HbA1c≥9.0% In addition, it has been suggested that household income is the major risk factor for depressive disorders [9]. In the United States the annual cost of DR rises to more than $500 million. Reasonably, the economic impact of the disease can add even more psychological burden among low-income patients. When depression occurs, additional health care cost emerges, further cultivating stress and leading to a vicious circle [9]. Interestingly, smoking seems to be a contributing factor for depression in patients with diabetes. It has been shown that in DM patients, smoking almost doubled the risk of depression. Collins also showed that smoking was independently associated with higher anxiety and depression scores in a cross-sectional study of 2049 individuals with type 1 or 2 diabetes conducting in Ireland [11].

On the other hand, depression itself is strongly linked with diabetes clinical course, as decidedly can impact diabetic regulation, adherence to treatment, and economic burden of the disease. Importantly, regarding adherence to treatment, there is evidence that the coexistence of DM and depression almost triples the possibility of lower adherence. In addition, depression is associated with higher levels of fatigue and anxiety, deteriorated quality of life, and more suicidal ideation [9].

A recent study evaluated the link between DR, disease severity and the manifestation of anxiety and depression. It demonstrated that patients with DR have a higher risk of a new diagnosis of depression, as well as that DR severity has a positive linear relationship with the depression occurrence. Of note, there was an increased risk of depression when disease progressed to PDR. Consistent with the findings regarding anxiety, the demographic with the highest risk of depression is patient's 18-34-year-old. However, in contrast with anxiety, the risk of depression remains heightened across all age's groups, even in the elderly, and it is not modified by DR severity. Sex-wise, men were shown to have higher risk of depression, which heightened depending on DR severity. In contrast, in women the crucial factor for depression

was only the presence or absence of DR [17].

Previous studies had shown that type 1 diabetes and PDR had higher risk of depression and to adverse daily life experiences compared to those with none or mild DR. Regarding the proliferative form, this finding was significant among those who had developed PDR in less than 2 years. The researchers had proposed that these patients may had more fluctuations in their visual acuity compared to those with longstanding DR and, therefore, thus being more vulnerable to depression occurrence. Another group showed that in patients with DR and low vision, fluctuating visual acuity associated with laser photocoagulation sessions or surgery had higher odds of depressive disorders compared to those with stable visual status [11]. A cross-sectional study in Australia included 519 patients with diabetes and showed that severe NPDR/PDR was independently associated with more intense depressive symptomatology after controlling for sociodemographic factors and clinical characteristics, including visual acuity. Notably, DME was not found to be associated with depressive manifestations. In this study, no association between DR and symptoms of anxiety was established [21].

Many epidemiological studies have also shown that women are at greater risk for major depression. Zhou X, et al. confirmed the finding in a Chinese population. This increased prevalence may be explained by the multifaceted role that women have to implement. The may have to deal with more stressful context trying to balance household and career, having simultaneously to face their own disease [9].

In contrast to the aforementioned findings, a number of studies do not confirm the association between PDR, visual impermeant and depression. In a cohort evaluating patients with 25 or more years of type 1 diabetes, not statistically significant findings were found. The authors suggested that depression may occurred after the development of diabetes because of the relatively young age at onset of diabetes. In this study only 4.15% manifested visual deteriorating in the 10-year period, suggesting that DR and visual statues remained in large part unchanged. Indeed, the mean visual acuity at the last follow-up visit after mean duration of diabetes of nearly 35 years, was remarkably excellent (20/20+1). The authors suggested that this high visual performance at the final point might be the explanation for the lack of correlation between visual acuity and depressive symptomatology in this cohort [11].

Laterality of Diabetic Retinopathy

In 2022, a cross-sectional study assessed the effect of DR on VR-QOL in patients with type 2 diabetes. Notably, bilaterality found to have a statistically significant impact on a wide spectrum of patients' performances, compared to those with unilateral disease. More specifically, patients with bilateral DR scored lower in a series of categories, including NEI-VFQ-25 dependency, general vision, mental health, near activities role completion [12]. An earlier study on patients of diabetes type 2 with DR, tried to evaluate the impact of DR and its severity on health-related quality of life (HR-QOL). The study found that participants with DR were compromised compared to participants without retinal findings and this association was impacted both by severity and laterality of disease. More severe DR had lower HR-QOL scores, as well as patients with bilateral DR compared to those with unilateral disease. The decline in HR-QOL in patients with DR occurred early in the disease process. The aspects with the most remarkable impact of DR were vision-related daily activities, dependency and mental health. The authors also showed that more severe DR was associated with lower general and vision-specific HR-QOL. More specifically, the impact DR severity was more prominent in driving ability, with the lowest QOL scores in the severe DR subgroup.

Of note, patients with bilateral moderate NPDR had the most significant compromise decrease in QOL compared to those with less severe DR. The authors underscored that across the spectrum of DR severity, the most significant differences were found between patients with unilateral versus bilateral moderate NPDR [7]. The message that should be conveyed regarding management of DR, is the necessity of developing appropriate screening, monitoring, and therapeutic approaches in order to avoid progression to bilateral moderately severe PDR form of the disease, positively affecting HR-QOL. For the time being, laser photocoagulation or vitrectomy are considered the most appropriate approaches in patients with severe NPDR to prevent the transition to PDR or severe ocular complications, such as neovascular glaucoma. However, given the aforementioned evidence regarding the significant burden that transition to bilateral moderately severe NPDR form of the disease bears, there are suggestions that favor an earlier intervention, as it is suggested that this severity level represents the threshold above which a significant compromise on a person's HR-QOL begins [7].

Diabetic Macular Edema and Anti-VEGF treatment

Diabetic macular edema represents the major chronic cause of visual loss in patients with DR regardless of disease's severity. There are findings supporting that visual deterioration secondary to DME and pending treatment anti-VEGF injections scored very poor regarding general health index of VFQ-25. As already mentioned, it seems that the level of retinopathy when DME is present, does not differentiate the VFQ-25 results. The authors underscored that the visual impairment secondary to DME contribute to general health compromise, rather than the diagnosis of DME or DR itself [22]. A study in 2023 showed that DME and treatment with anti-VEFG injections, as well as the number of doses, were significantly correlated with higher levels of anxiety [1].

Panretinal Photocoagulation in Diabetic Retinopathy

Panretinal Photocoagulation could have a potential role in modifying qualitative aspects in patients with DR. A study evaluated the quality of life and the factors in patients with DR before and after treatment with PRP. Generally, the findings confirmed that in DR patients, the severity of the disease, the level of visual acuity, as well as age, were all major constituents of an individual's QOL. The author came to the conclusion that even if PRP treatment could improve the mental health and social status of DR patients, it does not achieve improve the other aspects of visual function

[23]. A previous study had shown that PRP implementation was associated with lower scores the indexes of general vision, visual-depending tasks, driving and general health [15]. According to another group, previous laser treatment was linked with further deterioration in everyday life activities, general health, as well as visual status. Furthermore, regarding self-evaluation and self-confidence, 9 months after laser treatment, patients considered their sufficiency to complete tasks, worse compared to their status before therapeutic intervention [11].

Status of Employment

Regarding employment status, we have showed that working patients have significantly higher performances in many QOL indexes, including near and distance activities, peripheral vision, social functioning, mental health and dependency. Not surprisingly, employment positively affects patients' emotional status, motivating them improve their level of life [1]. Additional groups evaluated the association between employment, diabetes and depression. Studies have shown that unemployment can have a major impact on self-perception of non-vision-specific QOL [14]. Another study showed that the subgroup of patients who forced to quit job due to diabetic complications had double risk of 2 times depressive manifestations compared to those who quit job due to other reasons. In addition, patients with type 2 diabetes had higher rates of unemployment than those without the disease. In this subgroup unemployment also found to have the strongest link with depression [11]. It has been suggested that the burden of unemployment is heavier on a wide array of NEI-VFQ domains, including patients' well-being, mental health, interpersonal interactions and the ability to complete daily life tasks due to visual impermeant. Unemployment, especially among those of working age, represents a major emotional challenge [14]. The suggested impact of unemployment renders necessary the development of counseling programs for diabetic patients in order to learn how to deal with the stress that accompanies a status of not working [11].

Comorbidities, Insulin Treatment, Education Level and Sitting Habits

The presence of concomitant diseases, such as thyroid or heart disease, has been shown to be associated with significantly higher levels of anxiety. Additional comorbidities seem to constitute a psychological and emotional burden for patients with DR [1].

Regarding insulin, monotherapy or in combination, it was significantly linked with greater anxiety. Insulin treatment sparks the fear or/and pain that accompanies injections. In addition, patients who need insulin may are under stress associated with visual impermeant [1].

Education was also found to contribute positively to patients' well-being. More specifically, we showed that patients who were primary school graduates at most had significantly worse performance compared to those who were college/university or MSc graduates. It seems that individuals with higher level of education are more alert regarding potentially warning symptoms and signs of their general and visual health. In general, those patients tend to take better care of themselves as well [1].

Moreover, daily time spending seated seems to negatively affect composite VFQ-25 score, and more specifically, general health, general vision, distance activities, social functioning, and mental health. It has been suggested that sitting habit may promote introversion and lead to withdrawal from daily life activities, especially those demanding visual sufficiency. Sitting can also further compromise patients' general health, limiting the time spent on working out [24]. Working out and evolving in physical activities positively affect patients' QOL, strengthening the internal power of individuals and protecting them against emotional disturbances [1,8].

Conclusion

The presence of DR and especially progressed stages of the disease, negatively impacts patients' quality of life and emotional status. Usual constituents of normal daily life, such as self-sufficiency, come into question. Patients may face difficulties in a wide spectrum of everyday activities, including working, cooking, socializing, such as reading the newspaper, working, cooking, walking and driving. Unsurprisingly, patients potentially have to deal with psychological disturbances, like anxiety and depressive manifestation, in the context of emotional imbalance, adding an additional burden to patients' well-being.

Future Perspectives

The emerging impact of DR on the patients' well-being, quality of life and emotional status render DR and CME prevention, stabilization or delaying progression as a necessity in order to protect patients from manifesting psychological disturbances. A timely diagnosis with fundoscopy and subsequent stabilization of DR can positively affect the emotional and functional well-being of patients. Furthermore, the severity of DR could be a warning sign to prompt evaluation of emotional status in patients with more severe disease. On the other hand, the suggested bi-directional association between emotional disturbances and DR progression underscores the significance of taking into account the psychological constituents in order to delay DR worsening.

Regarding the proposed interventions, the purpose of DR therapy has been displaced from a single control of blood glucose and visual improvement, to an approach favoring the prevention of complications of the disease, as well as promoting a better quality of life. In our armamentarium anti-VEGF and PRP are at the forefront regarding treating the late complications of DR. However, in daily life reality, physicians and patients have often to deal with a crucial and challenging therapeutic context that is adherence to the strict use of medications and lifestyle changes. Patients face difficulties in altering years of habits and behaviors, leading to frustration and discouragement. In addition, it is well-established that medication adherence and lifestyle changes in general, factors crucial to the management of DR, are influenced by the patient's QOL. Furthermore, a diagnosis of anxiety or depression has

been shown to have negative implications on patients' QOL and adherence to medical treatment [25,26].

In addition, the monitoring of emotional status should be embedded in health care dealing with patients with DR. Many factors may have a significant impact on development of emotional disturbances, such as income, level of visual acuity, gender and previous treatments. The future goal is to utilize the understanding of how all these constituents interact with DR and psychological status, in order to develop the appropriate interventions to promote patient's visual stabilization/improvement and well-being. Awareness regarding the association between physical and mental health should be raised, leading to development of specially designed educational programs for DR patients with visual impermanent, especially when combined with low-income.

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