Article

Impact of the COVID-19 on the Control of Diabetic Patients in Diabetic Retinopathy and its Screening

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Abstract: (1) Background: Diabetic retinopathy (DR) is a complication of diabetes mellitus (DM) and the COVID-19 pandemic has affected screening programmes. The aim of present study was to determine the impact of the COVID-19 pandemic on the screening of diabetes patients in our Health Care Area (HCA); (2) Methods: A retrospective study of patients with DM who had attended the DR screening programme between January 2015 and June 2022. We studied attendance, DM metabolic control and DR incidence. (3) Results: Screening for DR decreased in the first months of the pandemic. Incidence of mild and moderate DR remained stable throughout the study, and we observed a little increase in severe-DR, proliferative-DR and neovascular glaucoma, during 2021 and 2022. (4) Conclusions: The COVID-19 pandemic caused a reduction in the number of patients screened for DM, although its effect on DR seems limited, with a similar number of patients with DR throughout 2015 to 2022, despite the number of patients with severe-DR and proliferative-DR increased in 2021 and 2022.

Keywords: telemedicine; diabetic retinopathy; diabetic macular edema; epidemiology; COVID-19

1. Introduction

In December 2019, a group of pneumonia cases were identified by genomic sequencing as a new coronavirus, SARS-CoV-2 [1] in the city of Wuhan (China). Due to the characteristics of this newly identified strain, its high communicability, spread, and risk of death, the WHO declared COVID-19 a pandemic on 30th January, 2020 [2]. The collapse of the health network together with the complete lockdown of citizens caused the suspension of all scheduled outpatient medical activity together with the relevant examinations for the diagnosis and monitoring of some pathologies.

Among such pathologies is diabetes mellitus (DM), a disease that has steadily increased worldwide for a number of years [3]. The latest report published by the International Diabetes Federation (IDF) estimates that 351.7 million people of active age (20-64 years) currently suffer with diagnosed or undiagnosed diabetes and is set to increase to an estimated 417.3 million by 2030 and 486.1 million by 2045 [4].

One of the complications of DM is diabetic retinopathy (DR), a microvascular complication and one of the main causes of blindness and preventable visual impairment in Europe today, especially when it develops to diabetic macular edema (DME) or proliferative-DR (PDR). These harmful effects of DM on vision have a significant impact on health spending and require screening programmes that allow regular monitoring, early detection, and timely treatment [5].

The COVID-19-19 pandemic has impacted in screening of DM patients, but depending on the fidelity of the patients to the screening system

 doi:10.20944/preprints202211.0274.v1

The aim of the present study was to determine the impact of COVID-19 on screening programmes for diabetes patients at our non-mydriatic fundus camera units at Hospital Universitario Sant Joan de Reus.

2. Materials and Methods

2.1. Study design

A retrospective study of patients with DM who had attended the DR screening units between January 2015 and June 2022 at Hospital Universitari Sant Joan de Reus, whose reference population is 200,318 inhabitants. Based on WHO estimates, the total number of DM patients in our health area could be 17,792. The present study included 16,152 patients with DM who had attended our DR screening programme during the study period, 98 of those with type 1 DM (T1DM) and 16054 with type 2 DM (T2DM).

2.2. Ethical adherence

This study adhered to legal requirements of our local ethics committee (approval CEIM 028/2018) in accordance with the revised guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

2.2. Inclusion criteria

Any patient with T1DM and T2DM controlled by the family doctors in our HCAs.

2.3. Exclusion criteria

Patients included in the group III of Diabetes. Other specific types (i.e. Diseases of the exocrine pancreas, Endocrinopathies, Genetic defects of ß-cell function, Genetic defects in insulin action). Patients included in the group IV of Diabetes. Gestational diabetes mellitus (GDM)

2.4. Objectives

To assess the impact of COVID-19 on the control of DM patients. To record the attendance numbers for DR screening during the period of the pandemic when the levels of glycaemia, HbA1c, systolic and diastolic blood pressure and degree of renal involvement through the value of the glomerular filtration rate were all determined. To record the incidence of patients with DR detected at our non-mydriatic camera units, and to determine the flow of patients with DR, classified according to the International DR guidelines.

2.5. Methods

This was carried out with one in initial retinograph of 45°, centred between the macula and the temporal side of the papilla. Diagnosis of DR was then made by three 45° retinographs according to the Joslin Vision Network (one centred on the macula, a second centred on nasal side of papilla, and a third centred at the temporal superior) using a Topcon NW400 retinal camera. The circuit and the technique is described in more detail elsewhere [6]. DR was diagnosed when microaneurysms were present in the fundus retinograph.

Because the opacity of the media makes it difficult to see the fundus, especially if only retinography is performed using a non-mydriatic camera, although the images with the new equipment have improved a lot, there are always around 3% of patients who do not visualize the queen well, in these cases what we have done is visit them in the ophthalmology service in person, even during the pandemic and resort to other diagnostic systems such as biomicroscopy, optical coherence tomgraphy (OCT), or angio-OCT.

DR severity was classified according to the International Council of Ophthalmology (ICO) [7] as: i) mild-DR with microaneurysms only, ii) moderate-DR (microaneurysms, hard exudates, haemorrhages and venous abnormalities), iii) severe-DR (the above together with one of the following: >20 haemorrhages in each quadrant, venous anomalies

 doi:10.20944/preprints202211.0274.v1

defined in 2 quadrants, intra-retinal microvascular abnormalities in 1 quadrant, no signs of proliferation, and iv) proliferative-DR, defined as the presence of neovascularisation. Neovascular glaucoma (NVG) is a severe form of secondary glaucoma characterized by a proliferation of fibrovascular tissue in the anterior chamber angle.

2.6. Studied risk factors

The epidemiological risk factors included in the study were, age and sex, duration of diabetes mellitus, arterial hypertension, which is indicated by a systolic/diastolic (normal value=140/90 mm Hg) measurement according to the report of the sixth joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure; and when the patient is taking anti-hypertensive medications. Levels of glycosylated hemoglobin (HbA1c) defined according to the American Diabetes Association recommendation [9 , 10], and the estimated glomerular filtration rate (eGFR), as measured by the chronic kidney disease epidemiology collaboration equation CKD-EPI, was estimated on urine collection.

2.7. Statistical analysis

Data was analysed using SPSS, version 22.0 (IBM® Statistics Chicago USA). The specific statistical study carried out and the specific type of test applied depended on the data obtained and its distribution.

For descriptive statistics, the mean, standard deviation, the 95% confidence interval for the mean, the median and the maximum and minimum values were used for quantitative variables. For qualitative variables, the absolute and relative frequencies and the percentages of each category were used.

The differences between two means were calculated by Student's t-test for independent samples (normal variable). Differences were considered statistically significant at $p < 0.05$. The comparison of more than two means was carried out through the analysis of variance (ANOVA, for normal variables).

3. Results

3.1. Evolution of the SARS-COV-2 pandemic

Firstly, we wanted to reflect on the impact that the pandemic caused by SARS-CoV-2 had on attendance at DR screening.

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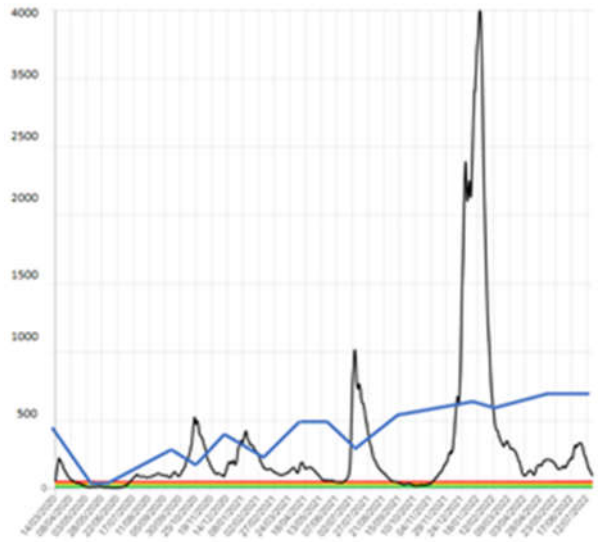

Figure 1. Weekly confirmed cases of COVID-19 in our Health Care Area in Catalonia (Spain) from March 2020 to June 2022, the image also shows together the percentage of patients with COVID-19 and attendance at DR screening. Blue line = Weekly confirmed cases of COVID-19 in our HCA from March 2020 to June 2022. Black line = Weekly attendance at DR screening from March 2020 to June 2022 in our HCA.

Figure 1 shows the evolution of the COVID-19 pandemic in our HCA from January 2020 to December 2021 (black line). It shows an exponential increase in cases in March 2020. However, it is necessary to take into account the poor diagnosis capacity of the first wave. As reported a posteriori by Health, the real incidence was estimated to be 10 times higher. From March to May 2020, because of the restrictions and confinement measures established by the State of Emergency, incidence decreased. Subsequently, a second wave was reported in November of the same year. The reduction of this wave was slower than the first wave and overlapped the third wave at the beginning of January 2021. The accumulated incidence was greater than in the first wave because of a better diagnosis capacity but there was better hospital care, leading to improved survival and better control of cases.

The last very high peak in the incidence of COVID-19, during January and February 2022 was due to the Omicron variant. Figure 1 shows, however, that this did not particularly impact DR screening. The latest data we have is from June 2022, as the other health authorities no longer report incidence.

In the eight-year period 1st January 2015 to 31st December 2021 we screened a total of 16,152 patients with DM (98 T1DM and 16054 T2DM). Each patient visited on average 2.38 times during the seven-year follow up.

Table 1. DR screening results, number of patients screened and percentage with respect to the total number of patients with DM in the study. 2022* data from January to June.

Year	Screened patients	Percentage %
2015	5996	37.12
2016	5801	35.91
2017	4911	30.40
2018	5933	36.73
2019	5741	35.54
2020	3286	20.34
2021	6104	37.79
2022*	2957*	19.30*

Table 1 shows the screening levels from 2015 to 2021. During 2020, attendance at screening units reduced and there was a significant increase the following year, 2021.

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The data in Figure 1 and Table 1 taken together show a reduction in 2020 in the total number of patients screened followed by a bounce back in the numbers in 2021, even higher than in the years prior to the pandemic. During the study period, there had never been more than 6000 patients screened in any given year until the peak in 2021.Demographic data of DR patients. The total number of DM patients screened was 16152, of which 8621 were male (53.38%) and 7530 were female (46.62%). Mean age was 67.93 ± 8.69 (12-89) years and mean DM duration was 9.09±6.79 (1-54) years. According to type of DM, 98 patients.

The greater number of males screened reflects the proportion of DM in the population. The statistical analyses showed no significant differences in the variables of sex, mean age, type, or duration of DM, were T1DM and 16054 were T2DM.

3.3. Demographic data of DR patients.

The total number of patients with DM screened 16152, which 8621 are males (53.38%) and 7530 are females (46.62%). Mean age was 67.93 ± 8.69 (12-89) years and mean DM duration 9.09±6.79 (1-54) years. According to type of DM 98 patients was type 1 DM and 16054 was type 2 DM.

The sample included a great prevalence of men, which is in consonance with the prevalence of diabetes in the population, it was not differences with respect to the sex prevalence along the study- Also, there are not significant differences according to the mean age. No differences on type of diabetic mellitus were significant along study. The DM mean duration, was similar along follow up. Differences of these four variables were not significant in statistical analysis.

Table 2. Description of HbA1c, arterial systolic and diastolic tension and eGFR estimated glomerular filtration rate along the seven years follow up study.

	2015	2016	2017	2018	2019	2020	2021	2022	p
Age	66.87 ± 8.57	67.02 ± 7.96	68.04 ± 9.12	67.12 ± 8.56	68.19 ± 8.77	66.97 ± 7.79	67.55 ± 8.02	68.01 ± 8.34	0.502
Sex (women %)	46.71	46.55	47.12	46.71	47.01	45.52	46.37	46.87	0.374
DM duration in years	9.11± 6.57	9.01± 6.78	9.12± 6.81	9.07± 6.85	9.13± 6.72	9.02± 6.78	9.15± 6.91	9.03± 6.98	0.324
HbA1c (%)	7.43 ± 3.09	7.47 ± 2.80	7.43 ± 2.57	7.46 ± 1.92	7.49± 1.72	7.51± 1.32	7.52± 1.68	7.47± 1.37	<0.001
eGFR (ml/min/1.73m²)	80.33± 23.56	81.29± 22.47	79.33± 24.33	80.23± 21.34	79.29± 23.56	81.36± 20.21	80.96± 24.81	80.66± 24.52	0.071
Annual number of analytics per patient	1.21	1.15	1.22	1.17	1.18	0.79	0.91	1.18	
Systolic arterial pressure (mmHg)	137.10± 12.90	135.97±15.29	134.20 ±20.11	136.20 ±18.3	136.11± 19.89	135.47± 20.53	134.50±23.33	134.50±21.67	0.134
Diastolic arterial pressure (mmHg)	79.97± 7.54	76.74± 7.20	78.40± 6.97	78.67± 7.27	79.18± 10.65	78.63± 11.48	77.92± 11.22	78.49± 11.21	0.087

Table 2 shows that only were significative the changes in mean values of HbA1c. The average HbA1c between 2015 to 2019 was 7.45±2.42% compared to 7.51±1.32% in 2020, 7.52±1.68% in 2021, and 7.54±1.37% in the first six months of 2022. Differences were measured by Student's t- test at a significance of p<0.001.

On the other hand, there were no statistically significant differences in age, sex, DM duration, mean glomerular filtration rate values and the mean values for systolic and diastolic blood pressure showed similar results.

Attending the number of tests per patient and per year, there was a mean of 1.18±0.28 (1.15 to 1.22) in 2015 to 2019 against 0.96±0.19 (0.79 to 1.18) in 2020 to 2022. A significant proportion of patients who should have attended in 2020 (we know who they were because they failed to be cited in 2020 and who did attend in 2021. In total, 1,097 patients in

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2020 were seen in 2021, that is, 17.97% of those seen in 2021 should have been seen in 2020. We have analyzed the data of these patients and they did not show a significant difference in factors of risk, age p 0 0.502, sex p= 0.374, DM duration p= 0.324, HbA1c p=0.103, eGFR p=0.230, systolic arterial pressure p=0.330 and diastolic arterial pressure p =0.304.

3.4. Diabetic retinopathy study.

Table 3 shows the incidence of DR in the screened patients. From 2015 to 2019 an average of 5676.40 ± 439.75 patients (minimum 4911, maximum 5996) patients were screened. This number dropped to 3286 in 2020, and recovered in 2021 to 6804, higher than the average of previous years. In the first half of 2022, 2957 patients have been screened, which suggests 5914 patients will be screened this year, a figure similar to that prior to the pandemic.

Table 3. Incidence of DR each year in the screened patients.

Year	Screened patients	Diabetic retinopathy patients	Percentage of DR respect to screened patients %
2015	5996	220	3,68
2016	5801	208	3,58
2017	4911	213	4,33
2018	5933	277	4,66
2019	5741	266	4,61
2020	3286	194	5,91
2021	6104	299	4,89
2022*	2957	139	4.70

Table 4. Classification of DR and its complications. * Number of patients, ** Percentage of patients with DR type versus number of patients screened this year.

		2015	2016	2017	2018	2019	2020	2021	2022*	p
DR classification	Mild	130* (2.16%)**	116 (1.99%)	110 (2.23%)	165 (2.78%)	138 (2.40%)	81 (2.46%)	135 (2.21%)	64 (2.16%)	0.017
	Moderate	47 (0.08%)	42 (0.72%)	49 (0.99%)	62 (1.04%)	81 (1.41%)	62 (1.88%)	66 (1.08%)	32 (1.08%)	0.023
	Severe	28 (0.46%)	37 (0.63%)	42 (0.85%)	36 (0.60%)	32 (0.55%)	36 (1.09%)	69 (1.13%)	26 (0.87%)	0.041
	Proliferative	15 (0.25%)	13 (0.22%)	12 (0.24%)	14 (0.23%)	15 (0.26%)	15 (0.45%)	29 (0.47%)	17 (0.57%)	0.037
DR complications	Diabetic Macular Edema	48 (0.8%)	49 (0.84%)	45 (0.91%)	44 (0.74%)	40 (0.69%)	19 (0.57%)	45 (0.73%)	23 (0.77%)	0.070
	Neovascular glaucoma	6 (0.10%)	5 (0.08%)	6 (0.12%)	4 (0.06%)	4 (0.06%)	5 (0.15%)	7 (0.11%)	3 (0.10%)	0.040

Table 4 shows the results of study of DR classification. From 2015 to 2019, the mean number with mild-DR was 131.80 ± 21.61 patients, a value that decreased to 81 patients in 2020, increased to 135 in 2021 and was 64 in the first six months of 2022. For moderate-DR, the mean was 56.20±15.7 affected patients, which increased to 62 in 2020, and to 66 in 2021, and there were 32 in the first six months of 2022, higher than the average of previous years but the results are not significant at p =0.023. The numbers for severe-DR were similar, with an average of 35±5.29 patients between 2015 and 2019, a decrease to 36 in 2020 and an increase to 69 in 2021. In the first six months of 2022, there have been 26 patients affected, which is also significant at p=0.041. For proliferative-DR, the average number of patients affected in the period 2015-2019 was 13.80 ± 3.60, increasing slightly to 15 patients in 2020 and more significantly to 29 in 2021. With 17 affected patients in the first six months of 2022, these changes are significant at p =0.037.

 doi:10.20944/preprints202211.0274.v1

Regarding the presence of diabetic macular edema (DME), the mean value from 2015 to 2019 was 45±3.60 patients, falling to 19 cases in 2021 and increasing to 45 in 2021, with 23 patients affected in the first six months of 2022. These differences are not significant at p= 0.07.

Finally, for neovascular glaucoma secondary to DR, an average of 5±1 patients were affected from 2015 to 2019, and in 2020 (5 patients), increasing to 7 patients in 2021 with 3 patients in the first six months of 2022. The differences between them were significant at p=0.04, but due to the small sample size they should not be considered representative of any possible changes due to the pandemic.

4. Discussion

The present study focused on the changes in DR screening during the COVID-19 pandemic in our HCA. The study shows a reduction in the number of patients attending during 2020 (Table 3). However, Figure 1 shows that fewer patients attended during March and April 2020, and numbers subsequently reduced a little each time there was a new wave of COVID-19. Screening numbers recovered in 2021 and again in the first half of 2022. In the year 2021 we have observed that 17.97% were patients scheduled for the year 2020 who did not attend their appointment, but a greater number of DR was not observed in these patients.

In total, at the end of the study we have observed that the COVID-1 pandemic) has not generated a greater number of patients with DR, but we did observe an increase in the years 2021 and 2022 of patients with severe-DR and proliferative-DR. Perhaps a worse control in a small number of patients during the pandemic, who already had worse metabolic control, have developed more serious forms that we have not been able to detect in time.

In relation to the metabolic control of the patients, we have observed worsened in the 2015-2019 group compared to the 2020-2022 period, as we showed in results, the mean levels of HbA1c were 7.45±2.42% in the first period (2015-2019) against an increases in 2020-2022 period (HbA1c= 7.51±1.32% in 2020, 7.52±1.68% in 2021) , decreasing again in the first six months of 2022 to values of 7.47±1.37%. These global data of all patients can give us a slight idea of what has happened in patients with DM during the pandemic, with worse control during the years 2020 and 2021 that is recovering in 2022, in any case they are data globally, individually there may still be large variations

A different approach to what has happened is through the number of control tests that patients with DM have carried out during the pandemic. In the current study we have determined the number of HbA1c data that we have obtained from the sample. Thus, the study shows a range from 1.18±0.28 (1.15 1.22) per patient extractions between 2015 to 2019, compared to 0.96±0.19 (0.79 to 1.18) per patient in 2020 to 2022. Only in the first six months of 2022 did they reach a number of HbA1c tests were similar to those prior to COVID-19. It is possible that the extractions were only performed in those patients with poorer glycemic control, unfortunately we do not have these data.

Attending DR type, the study shows an increase in crude data of patients with severe-DR and proliferative-DR in 2021, but in percentage the increase is not so important. We may suppose that patients with poorer DM control worsened during the pandemic and went on to develop severe-DR and proliferative-DR.

Respect to diabetic macular edema, there was no increase in the number of patients. Pre-pandemic, there were 40-48 patients diagnosed, reducing to only 19 patients in 2020 but recovering to pre-pandemic levels in 2021 with 42 patients, and 23 patients in the first six months of 2022. It is possible that diabetic macular edema requires other risk factors that have not been affected as much during the pandemic, such as the control of renal function, which in this study we have observed that the changes in eGFR have not been significant

There is no data in the current literature on the impact of COVID-19 on the screening of patients with DM. There have indeed been publications on how to react in the face of

 doi:10.20944/preprints202211.0274.v1

any future pandemic, following initial guidelines by the Royal College of Ophthalmology [11], who suggested that postponing DR screening might be necessary when facing severe staff shortages, a lack of personal protective equipment, and an escalation of infection numbers. At the beginning July 2020, Shih et al [12] reported that the default rate was especially high in February 2020, when there was widespread fear among patients of contacting COVID-19, although they report a slight improvement in March 2020. As of 12th April 2020, we had no reported cases of COVID-19 infection among our own clinical staff, nor among any patients who had undergone DR screening.

Also, there are publications, however, on the reduction due to the pandemic in the number of intravitreal injections in the treatment of patients with DME [13], which lead to vision loss in some patients who have not recovered their sight [14-16]. Furthermore, there have been numerous articles published on the importance of telemedicine in the control of patients with DM. Such system can detect the presence of DR as early as possible, especially for DME or severe- or proliferative-DR [17-21]. Similarly, the use of new AI technologies applied to DR diagnosis are being developed, driven by the pandemic [22, 23].

Regarding how the pandemic affected patients with DM, we do not know if other complications of it have changed during the pandemic period and we do not know the number of new patients, we only have data on the decrease in attendance at the screening system of DR and we only have the number of HbA1c per patient during the COVID-19 period, which actually decreased and therefore we can deduce that fewer tests were done per patient, which surely resulted in difficulties for the metabolic control of these patients.

The present study shows that having a telemedicine system strongly implanted in a health territory can reduce the effect of a new pandemic that makes it difficult for patients to be physically present during patient medical visits. In any case, we have to improve telemedicine systems since a not insignificant part of the patients studied worsened during the pandemic, surely those who were already poorly controlled.

Limitations of this study include following; first, in fact it was carried out in our own HCA, which is an area with great sensitivity towards DR screening both by patients and primary care physicians, as it was one of the first areas ever to implement a screening programme, in 2007 [24, 25]. It is therefore difficult to extrapolate our results to other areas of Spain, given the significant differences in the implementation of screening programmes in other health areas. Second, the study was based only on diabetic patients who were already diagnosed and who were known by the health system. We do not know what has happened in patients who were not diagnosed with diabetes during the covid period. Finally, we describe changes in screening program not the effect of pandemia in DR and DME treatment, patients described in the study are naïve and detected in screening, these patients were referred to the retina section of the hospital to be treated, and the objective of this study was not to determine the effect of the pandemic on the treatment of DR.

5. Conclusions

In the present study, we have observed that the COVID-19 pandemic decreased attendance at the DR screening program, and that in 2021 and 2022 study shows an increase of patients with severe-DR and proliferative-DR but poor significative.

Author Contributions: Conceptualization, P. R-A, M. B-B., E.GC. and R.S.; methodology, P.R-A. M.D., E.M., J.M., E.GC. .; formal analysis, P.R-A. M.D., E.M., J.M., M.V. and M.B-B..; resources, P.R-A and R.S..; writing—original and writing—review and editing, P.R-A. M.D., E.M., J.M., E.GC. and M. B-B., R. S-A.; visualization, P. R-A, M. B-B, E.GC.; supervision, and project administration, P.R-A. M.B-B, E.GC. and .S.; funding acquisition, P.R-A., R.S. and M.B-B All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Instituto de Salud carlos III, grant number PI21/00064 and FEDER funds.

Institutional Review Board Statement: This study was conducted in adherence to local legal requirements [local ethics committee of Hospital Universitari Sant Joan de Reus, approval no. 11-05-26/proj5].

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Acknowledgments: We thank all the patients as participants in the present study. We also thank Mr. Phil Hoddy for his language assistance and for editing and correcting the English text.

Conflicts of Interest: The authors declare no conflict of interest.

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