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ORIGINAL RESEARCH

Association between physical activity and severity of diabetic retinopathy in patients with diabetes mellitus

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Abstract

Background: Diabetes mellitus (DM) and its related complications such as diabetic retinopathy (DR) are among considerably growing global concerns. Many efforts have been done toward a better understanding of the modifiable risk factors of DR, to stop progression as well as prevention of this complication. Physical activity (PA) is a known modifiable risk factor of DM but its effect on the severity of DR is not clearly understood. In this study, we aimed to evaluate the association between PA and severity of DR.

Materials and Methods: A case-control study was done comprising 232 patients with DM (type 1 or 2), 58 of whom were in control group with no sign of DR, while the others were divided into three subgroups each contained 58 individuals, according to the severity of DR. PA of patients was assessed by the International Physical Activity Questionnaire (IPAQ) short-version and total scores of PA were compared among different groups.

Result: Total PA scores in (metabolic equivalent [MET]-hour/week) in control group, in patients with mild to moderate non-proliferative diabetic retinopathy (NPDR), severe to very severe NPDR, and proliferative diabetic retinopathy were 24.6 ±28.3, 23.7 ±30.6, 17.1 ± 27.0, and 7.1 ±10.2, respectively. The lower the score of PA, the higher the stage of DR ($r=-0.284$, $p<0.001$). Low PA levels came with higher stages of DR (odds ratio [OR]=2.7, P=0.023) than moderate PA (OR=2.1, P=0.114). When adjusted for age, sex, duration of DM, and type of medication regimen, the association of DR severity with PA level was still statistically significant in mild PA group (P=0.049) and statistically insignificant in moderate PA group (P=0.132). Adjusting for hemoglobin A1c (HbA1c) and body mass index (BMI) showed no significant correlation between PA level and DR severity (OR=1.1 and P=0.794 in low PA group, OR=1.2 and P=0.670 in moderate PA group).

Conclusion: Low PA level can be identified as a risk factor for DR, but not a completely independent one. It is more likely that PA lowers the risk of DR progression through lowering BMI and achieving better glycemic control (HbA1c).

Keywords: Body mass index, Diabetic retinopathy, HbA1c, International physical activity questionnaire, Physical activity.

Introduction

Diabetes mellitus (DM) is a considerably growing chronic disease, which had been estimated to affect 425 million adults (8.8% of individuals aged 20-79 years) globally in 2017, rising to 645 million by 2045. During years, noticeable efforts to diminish life-threatening complications of the disease and its related deaths, have led to increased life duration of patients with DM, which then faced the world with higher prevalence and greater burden of the disease complications and disabilities (1). It highlights the importance of paying more attention to diabetes complications and potential factors affecting them. Diabetic retinopathy (DR) is a major microvascular complication of DM, which is the leading cause of acquired vision loss in middle-aged economically active populations (2). Almost 34.6% of patients with diabetes have some degree of DR with 10% affected by visually threatening variants (3). Countries of the Middle East region including Iran, are among those with a rapidly increasing prevalence of diabetes. The prevalence of DR was reported in the range of 30–40% in most surveys of different regions of Iran (4). Clinically, DR is classified into two categories: non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). NPDR comprises mild microvascular changes (increased vascular permeability) to moderate and severe ones (capillary occlusion) which progresses to PDR causing retinal neovascularization and more prominent visual loss by subsequent vitreous hemorrhages or later tractional retinal detachments (5).

Low physical activity (PA) has been proposed as one of the modifiable risk factors of diabetes. Exercise training now plays a pivotal role in diabetes prevention and management and there are established guidelines defining suitable physical activity for patients with DM in detail (6). However, little is known about the associations between PA and severity of DR. Studies have reported various findings, some in line with a significant negative association between PA and DR severity (7,8), while some others declared no noticeable relation (9). On the other hand, despite the established hazardous impact of inactivity, it is not easy for large proportion of individuals to successfully adhere to public health recommendations of PA (10). A better understanding of various aspects of the relation between PA and DR may lead to wiser recommendations regarding PA and exercise to targeted groups of patients with DM who may benefit more. It can also help in designing more realistic efficient plans for better visual outcomes, slowing down the progression, lowering the financial, social, and personal burden of DR and even better response to current treatment modalities (7).

The purpose of this study was to evaluate the association between PA and DR severity in adults with DM with modifying some of the previous studies' limitations. To the best of our knowledge, no study has been performed by now, to evaluate this association in an Iranian population of patients with DM.

Materials and Methods

Study setting:

This is a case-control study, conducted between August 2018 and February 2019. Patients were selected from five distinct private and public ophthalmology centers located in Tehran, Iran. All eligible patients signed an informed consent form after explaining the purpose of the study to them.

Participants:

Patients with following criteria were included: 1) age between 30-69 years, 2) under treatment for diabetes type 1 or 2, 3) visual acuity between 20/200 and 20/20, 4) diagnosis of unilateral or bilateral DR (any stage of NPDR or PDR) with dilated fundus examination, 5) duration of diabetes between 10 to 30 years. The control group consisted of patients with DM with no evidence of DR in fundus examination, matched for the duration of diabetes.

Exclusion criteria for both groups were: 1) previous incisional ocular surgery, 2) positive history of retinal photocoagulation (pan-retinal and/or macular), 3) previous intravitreal anti-VEGF: Anti-vascular endothelial growth factor injections, 4) serious mental and/or systemic diseases and inability to respond to physical activity questionnaire, 5) systemic arterial hypertension, 6) smoking, and 7) prediabetes, gestational diabetes, or secondary diabetes (due to corticosteroid use, etc.)

Data collection:

Complete ophthalmic examinations including determining best corrected visual acuity

(BCVA), intraocular pressure, dilated fundus examination with slit-lamp biomicroscopy and with indirect ophthalmoscopy, were performed for all patients by a retina specialist who was not aware of patients' PA status. The severity of DR was determined according to the modified criteria of the Early Treatment Diabetic Retinopathy Study (ETDRS) (11).

All patients who met the inclusion criteria completed the Iranian version of the International Physical Activity Questionnaire (IPAQ), validity and reliability of which had previously been evaluated (12). The IPAQ short version consists of seven questions assessing walking, moderate-intensity activities and vigorous-intensity activities undertaken in domains including leisure-time PA, domestic and gardening activities, work-related PA, and transport-related PA in a typical week.

PA level was estimated by multiplying the duration (hour) per week of walking, moderate PA, and vigorous PA by their respective metabolic equivalent (MET); walking=3.3 METs, moderate PA= 4 METs, and vigorous PA= 8 METs. The sum of mild, moderate, and vigorous activity scores was calculated as the total PA score (MET-hour/week). Then, based on IPAQ measures, PA level was classified into three categories: low, moderate, and high.

Statistical analysis

Evaluated measures were expressed as mean and standard deviation, median and range, and frequency and percentage. The normal distribution of the quantitative variables was confirmed by Q-Q plot. To compare demographic variables between case and control groups, analysis of variance (ANOVA), Kruskal-Wallis test, Chi-Square test, and Fisher exact test were used, whenever appropriate. In the case of retinopathy and control comparison, these tests were *t* test, Mann-Whitney, Chi-Square, and Fisher exact tests. To obtain the relation between PA and outcomes, we used the Spearman correlation coefficient. To assess the relation between PA and DR, we used Binary logistic regression and presented its related OR with 95% confidence interval. In this model in addition to the crude model, we adjusted the effect of the possible confounders. In the last step, we considered the effect of BMI and HbA1c into the mentioned models to assess the possible effect of PA on DR severity from a different path than through BMI and HbA1c. All statistical analyses were performed by SPSS software version 25.0. (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). P values less than 0.05 were considered to be statistically significant.

Results

232 patients were enrolled in the study if they had the inclusion criteria. All of whom accepted to participate in the study. They were then allocated into four groups, each containing 58 patients. Group A were patients who were diagnosed with any stage of DR, divided into three distinct subgroups according to the severity of retinopathy: the first group consisted of patients with mild to moderate NPDR, the second group comprised patients with severe to very severe NPDR, and the third group consisted of patients with PDR. Group B included patients with no sign of DR who were considered as the control group.

The mean age of the participants was 52.8 years, 53% were men, and 3% had DM type 1. In the univariate analysis, case and control patients were similar with regard to age, sex, BMI, DM type, medication regimen of DM, duration of DM, and severity of PA of their jobs but different for HbA1c (table 1).

Total PA score (in MET-hour/week) was significantly different among control group (24.6 ±28.3, range: 0 to 120), patients with mild to moderate NPDR (23.7 ±30.6, range: 0 to 168), patients with severe to very severe NPDR (17.1 ± 27.0, range: 0 to 168), and patients with PDR (7.1 ±10.2, range: 0 to 54), ($p<0.001$). The Spearman correlation coefficient showed that the higher stage of DR was related to a lower score of total physical activity ($r=-0.284$, $p<0.001$).

Almost 43% of patients in the control group were reported to have low PA, while this amount was reported to be 31%, 63.8%, and 70.7% in patients with mild to moderate NPDR, patients with severe to very severe NPDR, and patients with PDR, respectively. Details of moderate and high PA in different groups of DR are presented in table 2.

Comparing the association between PA and DR severity showed that low level of PA is accompanied by more severe stages of DR in

comparison with high PA (odds ratio [OR]=2.7; 95% confidence interval [CI] 1.1–6.4), which was shown to be a statistically significant finding (P=0.023). Although moderate PA was also shown to come along with the higher stage of DR in comparison with high PA (OR=2.1; 95% CI:0.8–5.0), this difference was not statistically significant (P=0.114). Adjusting for confounding variables such as age, sex, duration of DM, and type of medication regimen, the association of low and moderate PA with DR remained the same in comparison with high PA regarding statistical significance (P=0.049 in low PA group and 0.132 in moderate PA group).

Eliminating the effect of HbA1c and BMI differences (mentioned as mediators) in case and control groups lowered the difference between DR severity in both low and moderate PA groups in comparison with high PA group and came with statistically insignificant results (OR=1.1 and P=0.794 in low PA group and OR=1.2 and P=0.670 in moderate PA group). This effect was remained while in the next step data were additionally adjusted for age, sex, duration of DM, and type of medication regimen as well as HbA1c and BMI. Table 3 displays the adjusted ORs and 95% confidence intervals.

Table 1: Characteristics of the patients included in the study

		Retinopathy				P	P2 (Control Vs Case)
		None	Mild to Moderate	Severe to very severe	Proliferative		
Age (years)	Mean ± SD	53 ± 6.5	51.8 ± 6.4	53.1 ± 5.2	53.4 ± 5	0.446†	0.825†
Sex	Male	31 (53.4%)	33 (56.9%)	28 (48.3%)	31 (53.4%)	0.830*	0.939*
	Female	27 (46.6%)	25 (43.1%)	30 (51.7%)	27 (46.6%)		
Height (Meter)	Mean ± SD	1.65 ± 0.08	1.69 ± 0.08	1.66 ± 0.07	1.67 ± 0.07	0.056†	0.107†
Weight (kg)	Mean ± SD	74.6 ± 10.5	75.1 ± 11.7	78.1 ± 12.5	79 ± 9.6	0.082†	0.093†
BMI	Mean ± SD	27.3 ± 3.6	26.2 ± 3.1	28.1 ± 3.2	28.5 ± 2.8	0.001†	0.500†
DM type	1	2 (3.4%)	4 (6.9%)	1 (1.7%)	0 (0.0%)	0.220**	>0.99**
	2	56 (96.6%)	54 (93.1%)	57 (98.3%)	58 (100.0%)		
Regimen	Oral medication	47 (81.0%)	35 (60.3%)	30 (51.7%)	36 (62.1%)	0.022*	0.004*
	Insulin injection	5 (8.6%)	8 (13.8%)	6 (10.3%)	4 (6.9%)		
	Oral medication +insulin injection	6 (10.3%)	15 (25.9%)	22 (37.9%)	18 (31.0%)		
DM Duration (years)	Mean ± SD	12.8 ± 3.5	13.5 ± 3.3	13.9 ± 3.3	14.2 ± 4.1	0.136‡	0.187‡
HbA1c (%)	Mean ± SD	7.69 ± 0.98	8.38 ± 0.98	8.82 ± 0.91	8.93 ± 0.91	<0.001†	<0.001†
Job***	Sedentary	42 (72.4%)	43 (74.1%)	48 (82.8%)	51 (87.9%)	0.337**	0.326*
	Moderate intensity	13 (22.4%)	12 (20.7%)	9 (15.5%)	5 (8.6%)		
	Severe intensity	3 (5.2%)	3 (5.2%)	1 (1.7%)	2 (3.4%)		

† Based on ANOVA for comparing the four groups and *t* test to compare the cases and control groups.
‡ Based on the Kruskal-Wallis test for comparing the four groups and Mann-Whitney test to compare the cases and control groups.
* Based on Chi-Square test.
** Based on Fisher exact test.
***Sedentary: such as office work.
Moderate intensity: requiring non-constant lifting, pulling, etc.
Severe intensity: requires nearly constant lifting, bending, etc.
Abbreviations: BMI: Body mass index; DM: Diabetes mellitus; HbA1c: hemoglobin A1c

Table 2: Results of IPAQ in the three groups of patients with DR and in the control group

		Retinopathy				rho§	P§
		None	Mild to moderate	Severe to very severe	Proliferative		
Physical activity score (Met/hour/week)	Mean Score ± SD	24.6 ± 28.3	23.7 ± 30.6	17.1 ± 10.2	7.1 ± 10.2	-0.284	<0.001
Physical activity level	Low	25 (43.1%)	18 (31.0%)	37 (63.8%)	41 (70.7%)	-0.279	<0.001
	Moderate	21 (36.2%)	30 (51.7%)	16 (27.6%)	15 (25.9%)		
	High	12 (20.7%)	10 (17.2%)	5 (8.6%)	2 (3.4%)		

§: Based on the Spearman Correlation coefficient.
Abbreviations: IPAQ: international physical activity questionnaire; DR: Diabetic retinopathy; Met: metabolic equivalent

Table 3: Relation between physical activity and diabetic retinopathy (odds ratio and 95%CI in Binary logistic regression)

Model	Physical activity level							
	Low				Moderate			High
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Unadjusted	2.7	1.1	6.4	0.023	2.1	0.8	5.0	0.114	Reference
Adjusted 1	2.8	1.2	6.6	0.021	2.1	0.8	5.1	0.110	Reference
Adjusted 2	2.5	1.0	6.1	0.049	2.0	0.8	5.2	0.132	Reference
Mediator only	1.1	0.4	3.2	0.794	1.2	0.5	3.4	0.670	Reference
Adjusted 1 + Mediator	1.2	0.4	3.4	0.723	1.3	0.5	3.6	0.609	Reference
Adjusted 2 + Mediator	1.2	0.4	3.6	0.693	1.4	0.5	3.9	0.532	Reference

Unadjusted: Crude relation of the PA and diabetic retinopathy stage.
Adjusted 1: Adjusted for the effect of age and sex.
Adjusted 2: Adjusted for the effect of age, sex, regimen, and diabetes duration.
Mediator: The effect of possible mediators (BMI and HbA1c) were considered in the model. These models investigate the effect of physical activity on diabetic retinopathy stages from a different path than through BMI and HbA1c.
Abbreviations: BMI: Body mass index; HbA1c: hemoglobin A1c

Discussion

In the present study, we evaluated PA level in patients with DM with different stages of DR and compared it with a control group of diabetic patients who had no sign of retinopathy. Our outcomes suggested that total PA was significantly lower in patients with PDR and severe to very severe NPDR as compared with patients with mild to moderate NPDR and to the control group. All four groups of patients had less high PA as compared with the low and moderate levels of PA. Patients with mild to moderate NPDR tended to have a moderate level of PA, while most patients with severe to very severe NPDR, as well as PDR had low PA, which was the most reported PA level in the control group, too. This finding can be interpreted better when considering a bidirectional relation between PA and DR stages, which means that while lower PA increases the risk of higher stages of DR, severe stages of DR may cause some limitations for patients to reach higher levels or even adequate level of PA. These barriers can be directly associated with vision problems or indirectly with other complications of DM, which decreases the capacity of patients for PA or even negatively influence on psychosocial aspects, keeping patients less outdoor and more willing to sedentary behaviors. So it seems PA and DR severity association may not solely be a causal

relation, but a bidirectional negative relation, which can trap patients in a vicious cycle.

We identified a negative correlation between DR severity and PA level, which was significant as low and high levels of PA were compared, but not statistically significant for the moderate level of PA compared with the high level. This finding indicates that suggesting increased PA with the aim of lowering the risk of DR deterioration should not necessarily be focused on the high level of activities in order to be effective, but encouraging the patients to reach the moderate levels of PA has adequate benefits in this regard. On the other hand, it may be more difficult for patients with low PA to maintain a daily program of longer duration or higher intensity of exercise and it is more feasible to keep a moderate level of PA. Besides, patients with uncontrolled proliferative retinopathy should avoid activities that increase the intraocular pressure and the risk of hemorrhage; hence low-impact activities are generally considered appropriate (13,14).

We found that the negative correlation between PA and DR severity is independent of age, sex, regimen, and diabetes duration, but is significantly affected by HbA1c levels and BMI. Though this negative correlation was reported when the effects of BMI and HbA1c levels were considered into account, it was of minor significance in groups with both low and moderate activities. Moreover, the difference between adjusted odds of low PA and moderate PA groups was lowered. So we concluded that lower PA increases the risk of DR severity through its effect on BMI and glycemic control.

The beneficial effect of PA on glycemic control has been reported in previous studies. Aerobic exercise apparently improves glycemic control in type 2 diabetes, especially when at least 150 min/week is done. Resistance exercise improves HbA1c in adults with type 2 diabetes by about 0.57% (15). Some studies have reported the HbA1c level as a predictor of PDR development (16), and some have suggested a direct relationship between HbA1c and DR severity (17).

Reporting the results of numerous studies evaluating the association between PA and DR in patients with type 1 and 2 DM are generally inconsistent. Some showed no significant association between PA and DR in patients with DM (9, 18-22), and some reported negative relation and protective effect (23-25). FinnDiane study group and Dirani and colleagues showed a significant association between low PA and higher incidence of proliferative DR in patients with type 1 DM (7,8). The protective effect of PA on DR has also been reported to be selective and only in a specific population in some studies. Cruickshanks and co-workers showed a negative relation between PA and PDR in only female patients who were diagnosed with diabetes prior to the age of 14 years (26). Loprinzi and others reported a significant association between advanced PDR and PA for women but not for men (27).

Inconclusive results regarding this relationship not only are seen in smaller studies, but also in larger epidemiological surveys. Moreover, some adverse events such as retinal hemorrhage have been attributed to heavy exercise in patients with DR (28). In an epidemiological study on the Japanese population evaluating the association of newly developed DR and PA, a meaningful reverse association was shown, independent of HbA1c and BMI (29). In another study performed on 320 patients in London, it was also reported that Increased PA was associated with less severe levels of DR, independent of the effects of HbA1c and BMI (23). Although the setting and design of the current study are similar to the recently mentioned study, the difference in reported results may partly be due to poor glycemic control and higher baseline of HbA1c level of patients in our study.

Conclusion

To the best of our knowledge, this is the first study to report the association between DR severity and PA level in an Iranian population. According to our results, we suggest that a low PA level can be identified as a risk factor for DR, but not a completely independent one. It is more likely that PA lowers the risk of DR progression through lowering BMI and achieving better glycemic control (HbA1c). We also state that the lower level of PA brings a significantly higher risk of advanced DR for patients with DM, while such a risk is lower and insignificant in such patients who maintain moderate PA.

In our study, PA was assessed with a questionnaire with established validity and reliability rather than objective measures. Although objective measures such as pedometer or accelerometer are not influenced by perception, they detect only ambulatory activities and also they are not useful for water activities. In addition, using a questionnaire is a more cost-effective way to estimate energy expenditure in a large population.

Limitations of this study are lack of longitudinal data, for which we could not state a definite causal relation between PA and DR. Further studies with longitudinal data are required to define such an association and investigate the way by which PA affects DR.

Conflict of interest

Authors declare no conflict of interest.

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