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Original Scientific Paper

THE IMPACT OF TOTAL PHYSICAL ACTIVITY ON MICROVASCULAR COMPLICATIONS IN TYPE 1 DIABETES MELLITUS PATIENTS

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SUMMARY – The incidence of diabetes is increasing worldwide, emphasizing an emerging need for blood glucose control optimization to prevent the development of chronic complications and improve the quality of life. This retrospective cohort study aimed to investigate the effects of total physical activity on microvascular diabetic complication development in patients with type 1 diabetes mellitus (T1DM). The study included 71 T1DM patients, average age 41 years and HbA1c 7.78%. Most patients (82.1%) reported having hypoglycemia, while the minority of patients developed microvascular complications, mostly nonproliferative retinopathy (17.7%). All subjects included in the study were moderately or vigorously physically active. No association was observed between total physical activity and regulation of glycemia, hypoglycemic incidents, or development of microvascular complications. Until sufficient data from prospective studies become available, our data support the findings of no negative effect of higher intensity physical activity on the development of microvascular complications in T1DM patients.

Key words: *Physical activity; Diabetes mellitus type 1; Microvascular complications; Hypoglycemia; Nonproliferative retinopathy; Proliferative retinopathy; Nephropathy; Albuminuria*

Introduction

Uncontrolled type 1 diabetes mellitus (T1DM) can lead to microvascular complications, while efficient blood glucose control can prevent or postpone their appearance[1]. In recent years, much attention has been given to the role of exercise in T1DM, which ensured a new concept for the treatment[2]. Nowadays, exercise therapy has a vital role in preventing and treating type 2 diabetes, while regular aerobic exercise has become a significant part of T1DM management[3-5]. Moreover, exercise therapy is used in adjunct to insulin and diet to prevent and treat cardiovascular disease and to reduce mortality. In T1DM patients, it is generally accepted that regular physical activity reduces the cardiovascular risk and insulin requirements, improves muscular strength and patient well-being[6]. The effects

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of physical activity on glycemic control and microvascular complications are still inconclusive[7,8]. According to some findings, children with T1DM should practice minimally three times weekly for at least 12 weeks of combined aerobic and resistance exercise to experience meaningful HbA1c reductions. Other studies suggest HbA1c elevations in patients who regularly exercise due to higher carbohydrate intake and hypoglycemia[9].

Duration of diabetes and poor glycemic control are the most common causes of microvascular complications in T1DM. The reported prevalence of neuropathy is 30%-60% and of advanced retinopathy 23%-59%, while diabetic kidney disease, defined as macro- or microalbuminuria, affects up to 30% of patients with T1DM. The mentioned microvascular complications, besides increasing the morbidity and mortality risk, significantly alter patient quality of life[10]. Studies regarding physical activity and risk of microvascular complications in T1DM are limited and their results are quite opposite, from those reporting worsening of neuropathy and retinopathy with exercise to those showing beneficial effects[1,2,11]. Moreover, evidence is still unclear whether the intensity of physical activity has an impact on complication-free life and longevity[12].

This retrospective case study and literature review tried to elucidate the effects of total physical activity on microvascular diabetic complication development and worsening in patients with T1DM.

Patients and Methods

This retrospective cohort study included 71 T1DM patients (34 women and 37 men) seen by attending diabetologists in 3 regional tertiary centers in Croatia during regular outpatient visits. T1DM was defined as a diagnosis of diabetes before age 40, and permanent insulin treatment was initiated within one year of the diagnosis. The Ethics Committee of the Faculty of Kinesiology, University of Zagreb approved the study protocol, and the investigation was conducted according to the Declaration of Helsinki. All patients gave their written informed consent. Included were patients who did not meet any of the following exclusion criteria: younger than 18 and older than 65 years, immobile due to diabetic neuropathy, patients who had suffered stroke, patients who had suffered myocardial infarction, amputated patients, patients with vertebral compressive fractures, blind patients, patients with untreated arterial hypertension, illiterate patients, and those who refused to sign the informed consent form.

We used the extended version of the validated International Physical Activity Questionnaire (IPAQ-LF)[13]. The questionnaire contains 27 questions to validate physical activity in the work domain, transportation habits, household-related activity, and physical activity during leisure time. The questionnaire was translated and validated in the Croatian language.

Statistical methods

Data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY, USA). Descriptive statistics was used to describe basic features of the study sample (proportions for categorical data, and mean ± standard deviation for normally distributed continuous variables, or median and interquartile range for variables deviating from normal distribution).

The selected metabolic equivalent of task (MET) values were derived from work undertaken during the International Physical Activity Questionnaire (IPAQ) Reliability Study conducted in the 2000-2013 period. Using the Ainsworth *et al*. compendium[13], an average MET score was derived for each type of activity. Median values and interquartile ranges were computed for walking (W), moderate-intensity activities (M), vigorous-intensity activities (V), and a combined total physical activity score. All continuous scores are expressed in MET minutes/week. For example, all types of walking were included, and an average MET value for walking was created. The same procedure was undertaken for moderate-intensity activities and vigorous-intensity activities. The following values continue to be used to analyze IPAQ data: Walking = 3.3 METs, Moderate physical activity (PA) = 4.0 METs, and Vigorous PA = 8.0 METs. Using these values, four continuous scores are defined: Walking MET-minutes/week = 3.3 * walking minutes * walking days; Moderate MET-minutes/week = 4.0 * moderate-intensity activity minutes * moderate days; Vigorous MET-minutes/week = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days; Total physical activity MET-minutes/week = sum of Walking + Moderate + Vigorous MET minutes/week scores.

Binary or categorical outcome variables were analyzed with the χ^2-test or Fisher exact test (alternative to the χ^2-test for 2x2 contingency tables). Independent t-test or ANOVA (2 or more groups) or Mann-Whitney U test was used for continuous variables. For repeated measures (paired samples), repeated-measures ANOVA for three measurements was used.

Results

The mean age of participants was 41.74 years, duration of diabetes was longer than 10 years in 44% of patients, and mean HbA1c was 7.78%. These data are shown in Table 1.

As many as 55 (82.1%) patients reported having hypoglycemia (Table 2). No macrovascular complications were diagnosed. The presence and frequency of microvascular complications are listed in Table 2. Only a minority of patients developed microvascular complications, mostly nonproliferative retinopathy (17.7%), followed by polyneuropathy (8.2%) and proliferative retinopathy (8.1%), while albuminuria and nephropathy were present in 6.7% and 3.2% of patients, respectively, and only one patient was on hemodialysis.

Data on physical activity levels according to the IPAQ results are shown in Table 3. All subjects included in the study were moderately or vigorously physically active.

There were no differences in the HbA1c levels according to high and moderate total physical activity (χ^2=0.688, Fisher exact p=0.663) (Fig. 1).

Table 1. Subject characteristics

Variable	Mean	SD	Median	Min	Max	n
Age (years)	41.74	13.36	41	19	68	68
HbA1c (%)	7.78	1.16	7.7	5.4	11	55

		n	%
Duration of diabetes (years)	≤10	20	31.3
	11-20	23	35.9
	≥21	21	32.8
Total		64	100.0

HbA1c = glycosylated hemoglobin A1c

Table 2. Frequency/presence of hypoglycemia and microvascular complications

Complication		n	%
Hypoglycemia	No	12	17.9
	Yes	55	82.1
Nonproliferative retinopathy	No	51	82.3
	Yes	11	17.7
Proliferative retinopathy	No	57	91.9
	Yes	5	8.1
Nephropathy	No	60	96.8
	Yes	2	3.2
Albuminuria	No	56	93.3
	Yes	4	6.7
Hemodialysis	No	60	98.4
	Yes	1	1.6
Polyneuropathy	No	56	91.8
	Yes	5	8.2

Table 3. Descriptive parameters of particular physical activity domains and levels

Intensity and type of physical activity	Mean	SD	Median	Min	Max	n	p
Work walk TOT	971.87	1357.91	396	0	7623	71	0.004
Work moderate TOT	702.25	1183.75	0	0	5040	71	0.000
Work intense TOT	364.51	1061.85	0	0	7200	71	0.000
Work TOT	**2038.63**	**2759.60**	**996**	**0**	**15210**	**71**	**0.052**
Transport walk TOT	434.11	599.97	198	0	2772	71	0.000
Transport bike TOT	67.61	221.25	0	0	1080	71	0.000
Transport TOT	**501.72**	**646.48**	**247.5**	**0**	**2772**	**71**	**0.000**
Home/Garden intense TOT	381.90	814.03	0	0	3960	71	0.000
Home/Garden moderate TOT	692.68	869.54	480	0	4320	71	0.002
Home moderate TOT	536.83	697.02	360	0	3780	71	0.000
Home/Garden TOT	**1611.41**	**1801.50**	**1080**	**0**	**9000**	**71**	**0.001**
Leisure walk TOT	881.24	850.22	594	0	3465	71	0.001
Leisure moderate TOT	317.18	478.35	0	0	2520	71	0.000
Leisure intense TOT	396.62	761.19	0	0	2880	71	0.000
Leisure TOT	**1595.04**	**1560.49**	**1314**	**0**	**8172**	**71**	**0.040**
Sitting time TOT	1894.93	1077.73	1740	0	4140	71	0.676
Sitting AVG Week	270.70	153.96	248.57	0	591.43	71	0.676
Total moderate MET min/wk	**2698.45**	**2284.91**	**2460**	**0**	**11100**	**71**	**0.039**
Total vigorous MET min/wk	**761.13**	**1284.78**	**0**	**0**	**7200**	**71**	**0.000**
Total physical activity MET-min/wk	**5746.80**	**3634.25**	**5192**	**0**	**16248**	**71**	**0.778**

TOT = total; AVG = average; MET = metabolic equivalent of task

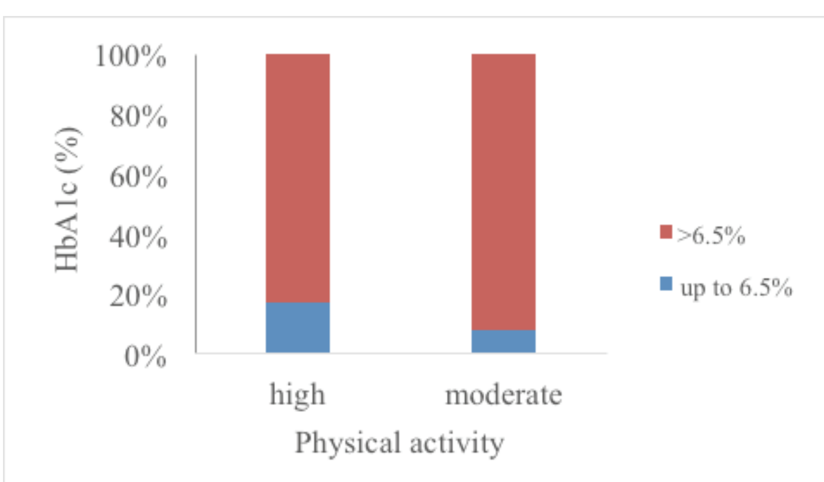

Fig. 1. Association of total physical activity with HbA1c levels.

Table 4. Correlation of total physical activity and hypoglycemia

Total physical activity	t	df	p (T test)
Walking MET min/wk	-0.408	65	0.685
Moderate MET min/wk	1.372	65	0.175
Vigorous MET min/wk	-0.109	65	0.914
Total physical activity MET min/wk	0.598	65	0.552

MET = metabolic equivalent of task

Table 5. Correlation of total physical activity and microvascular complications

Complication	Total physical activity			p (Fisher exact test)
		High	Moderate	
Retinopathy	No	75.0%	85.7%	0.497
	Yes	25.0%	14.3%	
Kidney complications	No	91.1%	100.0%	0.575
	Yes	8.9%	-	
Polyneuropathy	No	94.6%	85.7%	0.260
	Yes	5.4%	14.3%	
All microvascular complications	No	75.0%	71.4%	0.745
	Yes	25.0%	28.6%	

Total physical activity did not correlate with hypoglycemia (Table 4).

There was no correlation between total physical activity and presence of microvascular complications either (Table 5).

Discussion

Physical activity is an integral part of diabetes management and offers many health benefits. However, there is insufficient evidence for the beneficial effects of physical activity on the severity of microvascular complications. In addition, a significant risk of hypoglycemia raises concerns about the safety of regular exercise[5]. For T1DM patients, it was previously shown that the total amount of physical activity (in particular leisure time activity) was inversely related to mortality risk[14]. Data from the trials on diabetic kidney disease in T1DM support the relationship between a reduced intensity of leisure-time physical activity in patients with micro- compared with normoalbuminuria, suggesting that low intensity physical activity might precede microalbuminuria as the conventional clinical sign of kidney injury[1]. Moreover, data generated from the prospective FinnDiane Study further support the causal relationship between the high-intensity leisure-time physical activity and prevention of development and progression of diabetic nephropathy in T1DM patients[11]. Although the connection between physical activity and risk of diabetic retinopathy has been under scrutiny of different observational studies, so far, no clear relationships have been found. The Pittsburgh Insulin-Dependent Diabetes Mellitus Morbidity and Mortality Study was among the first studies that initially and in the 5-year follow-up found the protective trend in individuals participating in team sports but failed to show statistically significant associations between physical activity and diabetic retinopathy. In contrast, the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that participation in high school team sports was associated with a lower incidence of diabetic retinopathy in a subgroup of female patients diagnosed with diabetes under the age of 14[15,16]. On the other hand, a cross-sectional Finnish study demonstrated an association between low-intensity physical activity with proliferative retinopathy[17]. More recently published data resulting from 10-year follow-up revealed inverse correlation of the frequency of physical activity with the severity of diabetic retinopathy regardless of patient sex, and at the same time found no association between total physical activity, or single session duration or intensity of activity with the severity of retinopathy. In fact, in the higher-intensity groups, the cumulative incidence of severe diabetic retinopathy was even higher, although not statistically significantly[18]. Moreover, guidelines are supporting the need of special caution regarding diabetic retinopathy, since excessive exercise may lead to worsening of severe nonproliferative and unstable proliferative retinopathy, and increase the risk of fundus hemorrhage and retinal detachment[6,19,20]. On the other hand, diabetic foot ulcers, a major consequence of distal polyneuropathy, are among the most serious complications of diabetes and a major cause of lower limb amputations. Several studies report on a beneficial effect of exercise on diabetic foot-related outcomes, irrespective of exercise type[21,22]. Regular physical activity improves the function of peripheral sensory nerves and their conduction characteristics, thus positively affecting the incidence of ulcers in the exercise group compared with the control group, as suggested by Matos *et al.*[23]. It has also been shown that running, cycling, and brisk walking alleviates the symptoms caused by peripheral nerve injury and effectively reduces blood glucose and glycated hemoglobin, thus improving the quality of life of diabetic peripheral neuropathy patients[24]. However, due to reported musculoskeletal problems, increased wound size, and amputation associated with exercise, further studies are needed to assess the potential harms of exercise on diabetic foot ulcers[25]. In patients with diabetes with autonomic neuropathy, clinical manifestations such as decreased heart rate, decreased cardiac output, abnormal sweating, and impaired gastrointestinal function often worsen after exercise[26]. The most common manifestation of diabetic autonomic neuropathy relates to cardiovascular autonomic neuropathy. It is defined as impairment of autonomic control of the cardiovascular system in diabetes environment after excluding other causes. Although there is a significant association between cardiovascular autonomic neuropathy and increased mortality, there is no effective therapy to prevent this condition besides symptomatic management and glycemic control[27]. In fact, numerous studies have shown that hypoglycemia may elevate reductions in heart rate variability in diabetic patients[28-30]. Moreover, it has been reported that increased glucose variability, especially with overcoming the hypoglycemic stress, was associated with numbness in measures of heart rate variability in T1DM patients[31,32]. These data support the potential role of hypoglycemia in the development of cardiovascular autonomic neuropathy and loss of protective cardiovagal mechanisms, which can significantly affect the cardiac electrical activity and ultimately increase the risk of cardiac arrhythmias in T1DM patients. However, available data suggest that long-term and regular high-intensity training restores cardiovagal activity and has beneficial effects on cardiac autonomic function in type 2 diabetes patients, but in T1DM patients, data are scarce, and further studies are needed[33-36].

In our study, no association was observed between total physical activity and regulation of glycemia, hypoglycemic incidents, or development of microvascular complications. This can be explained by the fact that all patients in our study were moderately to intensely physically active; therefore, comparing inactive or less active in relation to moderately/intensely physically active was not possible. Most of our patients had hypoglycemia, more than 80%, but a relatively small number of patients had developed microvascular complications despite quite long diabetes duration (more than 60% of patients had diabetes duration over 10 years), which can again be explained by the fact that all included patients were moderately to intensely physically active, which confirms the hypothesis of a beneficial effect of physical activity on the development of microvascular complications. Given the nationwide approach, and the use of standardized questionnaire assessing physical activity level in different domains (work, transportation habits, household-related activity, and leisure time physical activity) and components of physical activity (intensity, frequency, and duration), our study adds information to the limited and somewhat confusing availability of data on physical activity and microvascular complications in T1DM patients. Furthermore, hypoglycemia does not appear to affect total physical activity, at least not in our patient population, indicating that most patients successfully cope with the fear of hypoglycemia and find appropriate methods to avoid hypoglycemia including increased carbohydrate intake, insulin dose adjustment, and duration and type of exercise. Also, increasing availability of technology-based tools such as insulin pumps, flash or continuous glucose monitoring systems, closed loop hybrid systems are allowing impossible to become possible, i.e., regular exercise activity with strict glycemic control with minimum or no fear of hypoglycemia and life free of long-term complications.

However, the observational nature of the study, self-assessment of physical activity by a questionnaire leading to potential over- or underestimation, and the small number of subjects do not allow general conclusions. Besides, all patients in the cohort were moderately or vigorously physically active, which prevented comparison with the inactive or less active population.

Conclusion

Exercise therapy, complementing conventional insulin therapy in patients with T1DM, could alleviate microvascular complications and thus improve their quality of life. Moderate or vigorous physical activity can counteract metabolic defects leading to the development of complications. Available evidence so far supports the notion to endorse regular exercise and improve cardiorespiratory fitness in the treatment of T1DM patients. Nonetheless, high-quality structured exercise programs in T1DM are needed to elucidate the association of physical activity and development of microvascular complications.

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Sažetak

UČINAK UKUPNE TJELESNE AKTIVNOSTI NA MIKROVASKULARNE KOMPLIKACIJE U BOLESNIKA S DIJABETESOM TIP 1

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Učestalost šećerne bolesti globalno raste, što naglašava potrebu za optimizacijom kontrole glukoze u krvi kako bi se spriječio razvoj kroničnih komplikacija i poboljšala kvaliteta života. Cilj ove retrospektivne kohortne studije bio je istražiti učinke tjelesne aktivnosti na razvoj mikrovaskularnih dijabetičkih komplikacija u bolesnika s dijabetes melitusom tip 1 (T1DM). U studiju je uključen 71 bolesnik s T1DM prosječne starosti 41 godina i HbA1c od 7,78%. Većina bolesnika (82,1%) imala je hipoglikemiju, dok je kod manjeg broja bolesnika došlo do mikrovaskularnih komplikacija, uglavnom neproliferativne retinopatije (17,7%). Svi ispitanici uključeni u istraživanje bili su umjereno ili intezivno tjelesno aktivni. Nije primijećena povezanost između ukupne tjelesne aktivnosti i regulacije glikemije, hipoglikemijskih incidenata ili razvoja mikrovaskularnih komplikacija. Sve dok ne postanu dostupni dovoljni podaci iz prospektivnih studija, naši podaci potkrepljuju dokaze da nema negativnog učinka intenzivnije tjelesne aktivnosti na razvoj mikrovaskularnih komplikacija u bolesnika s T1DM.

Ključne riječi: *Tjelesna aktivnost; Dijabetes tip 1; Mikrovaskularne komplikacije; Hipoglikemija; Neproliferativna retinopatija; Proliferativna retinopatija; Nefropatija; Albuminurija*