

The predictors of exercise capacity impairment in diabetic patients

Florina Frîngu¹², Gabriel Gușetu¹², Adriana Iosip¹², Diana Gurzău¹², Gabriela Dogaru¹, Dumitru Zdrenghea¹², Dana Pop¹²

1. University of Medicine and Pharmacy "Iuliu Hațieganu"

2. Department of Cardiology, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania

ABSTRACT

Background. The exercise capacity is a key issue in a diabetic patient's management, due to its well-known beneficial effects in terms of glycemic control, cardiovascular risk reduction and quality of life improvement. However the exercise capacity of diabetic patients is decreased many times and its determinants are sometimes less known. Our study aimed to assess the effort capacity in a cohort of diabetic patients and to find the main causative factors of its impairment.

Method: 61 patients with type-2 diabetes mellitus were enrolled and underwent transthoracic echocardiography and a cycloergometer exercise testing. Exercise performance was calculated and the influence of clinical data and ultrasound parameters was assessed. Sedentary status of each patient was established from total time/week of at least moderate physical activity.

Results: the study group consisted of 48.4 % women, mean age 61.4 (± 8.4) years. Disease median duration was 5 years and 21.3 % of the patients presented neuropathy, 4.5 % retinopathy and 6.5 % nephropathy. Exercise capacity was moderately and severe decreased (<5 METs) in 37.7 % of patients and in this subgroup the diastolic dysfunction, sedentary behavior and old age has a significantly higher prevalence. Interestingly, by multivariate regression, the sedentary lifestyle was the main determinant of decreased effort capacity (beta-coefficient 1.37, $p < 0.001$), suggesting the potential benefits of physical training in these patients.

Conclusion. Our study found a decreased effort capacity in at least one third of the patients and this is mainly due to sedentary lifestyle and deconditioning, the diastolic dysfunction also contributes to decreased effort capacity in diabetic patients.

Keywords: diabetes mellitus, exercise performance, diastolic dysfunction, exercise testing

Introduction.

Type 2 diabetes is a growing health issue in Western Countries and its morbidity is mostly related to cardiovascular involvement. The disease is diagnosed in 366 billion people (56 million cases in Europe) and it is estimated to encounter about 522 billion in the year 2030 [1].

Regular physical play a key role not only in glycemic control [2], but also in improving lipidic profile [3], reducing visceral adipose tissue and insulin resistance and finally decreasing the cardiovascular risk (which is two times higher in the presence of diabetes) and mortality.

All the beneficial effects of exercise are independent of age and gender. They are reversible and reproducible [4].

Diabetes represents a unpleasant psychosocial situation that affects the quality of life due to insulin administration, dietary monitoring, blood sampling for glycemia measurement. The lower level of quality of life impaires the degree of happiness, favors depression, decrease the labor participation rate and treatment compliance.

Accordingly the addition of a regular exercise regimen to drug treatment increases not only the life expectancy but also improves the quality of life [5,6], which is of utmost importance in the global management of diabetes.

Nevertheless, the exercise level in diabetic persons is decreased and the causative factors identification play is a key point before the initiation of an educational

program targeting the nonpharmacologic control of disease.

That's why the present study aims to assess through a standard exercise stress testing, the effort capacity in a cohort of diabetic patients without cardiovascular disease and to identify its main determinants.

Method

Patients. The study included 61 patients with type 2 diabetes mellitus (DM2) admitted in the Department of Cardiology-Rehabilitation Cluj-Napoca. All DM2 patients fulfilled the American Diabetes Association diagnosis criteria [7]. Patients with any signs, symptoms or ECG changes of a cardiovascular disease were excluded. We also ruled out the patients with neurological, respiratory, liver or kidney disease which could contraindicate or impair the exercise testing results. Patients with joint degenerative conditions limiting the proper cycling during testing were also excluded.

The study was conducted in accordance with the Declaration of Helsinki for human studies and was approved by the institutional ethical committee. All patients gave a signed informed consent to participate in the study.

Study design. Between Jan 2106 and December 2016 the patients were evaluated in terms of DM2 history, other cardiovascular risk factors (smoking, obesity, dyslipidemia, arterial hypertension), history for cardiovascular disease, a standard (12-lead) electrocardiography (ECG) and biochemistry data obtained by local laboratory. The sedentary status of each patient was established if total time of moderate physical activity was < 150min/week . All patients were further evaluated by a standard Doppler echocardiography and an exercise stress testing on cycle-ergometer.

Echocardiography. The transthoracic echocardiography was performed on the left lateral decubitus using a 3.5 MHz transducer on an *Philips Affinity 70* echo machine. Long axis, short axis, two chamber and four chamber views were obtained in order to perform M-mode and B-

mode (2D) measurements of chamber diameters and volumes and left ventricle ejection fraction (LVEF). LVEF was calculated using the modified Simpson's method from a four-chamber apical view.

Left ventricular diastolic performance was assessed by pulsed-wave Doppler measurement of the mitral E (early diastolic) and A (late diastolic) inflow velocities. The E/A ratio and deceleration time (DT) of the early filling velocity were also recorded. Additional mitral annular septal early (E'_s) and late (A'_s) diastolic velocities were assessed by tissue Doppler imaging. The E/E' ratio was calculated in order to estimate the LV filling pressure and to distinguish a normal inflow pattern from pseudonormal LV filling (both with an E/A ratio = 0.8-1.5). DD was categorized in three stages [8]: normal (E/A ratio = 0.8-1.5, DT=160-200 ms, $E'_s \geq 8$ cm/s, $E/E'_s < 8$), 1st degree (E/A ratio < 0.8, DT > 200 ms, $E'_s < 8$ cm/s, $E/E'_s < 8$), 2nd degree (E/A ratio = 0.8-1.5, DT=160-200 ms, $E'_s < 8$ cm/s, $E/E'_s = 9-14$), 3rd degree (E/A ratio > 2, DT < 160 ms, $E'_s < 8$ cm/s, $E/E'_s \geq 15$). According to these parameters, the patients were assigned in one of the three DD stages.

Exercise stress testing. DM2 patients also performed a standard exercise stress testing on cycloergometer, using the 25W / 3 min *step* protocol. The maximal workload (W), blood pressure and heart rate, continuous 12-leads ECG monitoring were recorded and analyzed on a *Cardiax 3.1* for Windows software. Maximum exercise capacity was calculated and expressed as METs.

Statistical analysis was carried out using the Microsoft Excel 2007 and SPSS for Windows (v 20.0, IBM Corporation, USA) software programs. The results were presented as numbers and percentages for qualitative variables and, for quantitative variables as mean \pm standard deviation; for nonparametric variables, median and range was used. In order to assess the normal (parametric) distribution of continuous numerical variables, the Kolmogorov-Smirnov test was used. To compare the

qualitative variables (frequencies), the chi-squared (χ^2) test was used. The analysis of quantitative variables with normal distribution was carried out using the Student t-test (t); for nonparametric variables the Mann-Whitney test was applied. A value of $p < 0.05$ was considered statistically significant.

Results.

Demographic and personal history data are presented in table 1.

Table 1. The demographic data and the clinical characteristics of the patients IQR, interquartile range; SD, standard deviation.

Patients, n	61
Female gender, n (%)	30 (48.4)
Mean Age, years (\pm SD)	61.4 (8.4)
Disease duration, years (IQR)	5 (7)

The mean age of the patients was 61.4 ± 8.4 years, and 30 of these (48.6%) were women. The duration of the disease ranged between “new diagnosed” and 20 years, with a median value of 5 years. On oral antidiabetic medication were 63.4% of patients, 18 % on insulinotherapy (alone or combination) and 21.3% of them followed diet treatment only.

Treatment groups, n (%)	
Diet only	13 (21.3)
Oral medication	39 (63.4)
Insulin	11 (18)
Disease complications, n (%)	
Retinopathy	3 (4.5)
Nephropathy	4 (6.5)
Neuropathy	13 (21.3)
Multiple	3 (4.5)
Associated CVRF, n (%)	
Hypertension	60 (98.3)
Dyslipidemia	13 (21.3)
Smoking	10 (16.4)
Obesity	40 (65.5)
Class I	24 (39.3)
Class II	13 (21.3)
Class III	3 (5)
Sedentary status, n (%)	
Active	26 (42.6)
Sedentary	35 (57.4)

The complications were recorded in 4.5% (retinopathy), 6.5% (nephropathy) and 21.3% (neuropathy).

Among cardiovascular risk factors hyper-tension encountered a 98.3% and obesity 65.5% (table 1), both of them recognized to impair exercise performance.

Table 2. The main parameters of cycloergometer exercise testing

	Exercise capacity impairment		p-value
	Moderate/ severe	Normal or mild	
Patients, n	23 (37.7)	38 (62.3)	-
Age, years**	65.2 (7.8)	59.2 (8.1)	0.011
Disease duration, y*	6 (6)	5 (7)	0.43
Neuropathy, n (%)***	4 (17.4)	9 (23.7)	0.404
Dyslipidemia, n (%)***	21 (91.3)	27 (71.1)	0.06
Smoking, n (%)***	4 (17.4)	6 (15.8)	0.56
BMI, Kg/m ² *	33.1 (4.5)	31.6 (3.9)	0.18
Sedentarism, n (%)***	21 (91.3)	14 (36.8)	<0.001
Double product, mmHg/min**	20 898	24 782	0.008
LVEF, %*	59.3 (7.8)	62.63 (7.5)	0.121
Diastolic dysfunction, n (%)***	18 (78.3)	21 (55.3)	0.05

* expressed as median (IQR) ** expressed as mean (\pm SD)

HR, heart rate; SBP, systolic blood pressure; METs, metabolic equivalents; IQR, interquartile range; SD, standard deviation.

The exercise testing parameters are presented in table 2 and generally reflect a slight decrease of effort performance (mean value 5.3 METs). Based on calculated effort capacity (METs) we divided the patients into two subgroups, with moderate-to-severe impaired exercise capacity (<5 METs) and with normal or mild decreased effort capacity (≥ 5 METs) (figure 1).

The mean age, diastolic dysfunction prevalence and sedentary status were significantly different in the two subgroups (table 3). Conversely, the diabetes duration, and other cardiovascular risk factors did not differ among these two subgroups. De double product (max blood pressure multiplied by max heart rate) was

significantly decreased in the first subgroup ($p=0.008$), even if the mean value was above 22 000 in the entire studied group.

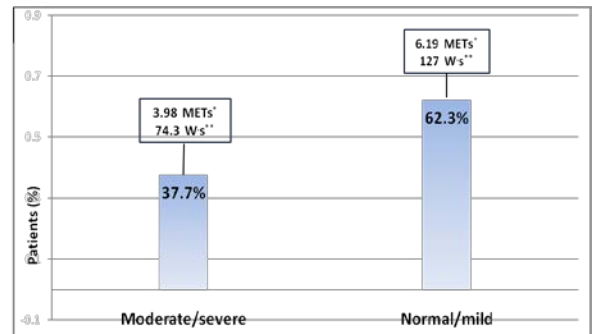


Figure 1. The distribution of the patients in the two subgroups (“moderately to severe impaired” vs “preserved” effort capacity) and main exercise test parameters

Table 3. The correlation between exercise capacity, disease characteristics and cardiac ultrasound parameters

	Exercise capacity impairment		p-value
	Moderate/ severe	Normal or mild	
Patients, n	23 (37.7)	38 (62.3)	-
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Diastolic dysfunction, n (%)***	18 (78.3)	21 (55.3)	0.05

* expressed as median (IQR) ** expressed as mean (\pm SD) *** expressed as percentage within each subgroup

BMI, body mass index; LVEF, left ventricle ejection fraction, IQR, interquartile range; SD, standard deviation

In order to assess the strength of each of the three determinants (age, diastolic dysfunction and sedentary status) we performed a multivariate linear regression analysis and the sedentary status seems to be the main factor related with impaired

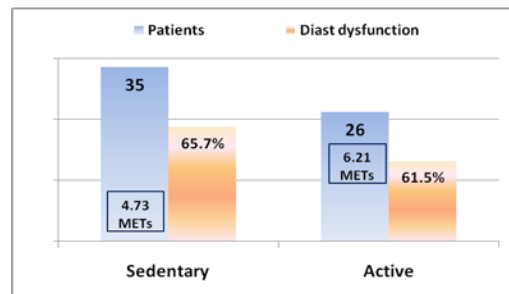
exercise performance (beta-coefficient=1.3- table 4). Moreover, the diastolic dysfunction has similar prevalence in the subgroup of sedentary and active patients (figure 2).

Table 4. The multivariate linear regression analysis for exercise capacity determinants.

Variable	B-coefficient	Std. Error for B	Significance
(Constant)	7.827	1.046	0.000
Sedentarism	1.376	.267	0.000
Diastolic dysfunction	-.715	.217	0.002
Age	-.041	.016	0.012

Dependent Variable: METs

Figure 2. The diastolic dysfunction prevalence is similar among sedentary and active individuals. Active individuals have a better exercise capacity



Discussion.

Our study has shown the effort capacity is significantly decreased in more than one third of diabetic patients without clinical signs and ECG evidences of cardiac disease. Ivanova et al also reports a decreased exercise participation among diabetics as a consequence of anxiety or depression, common among these patients. Further, less exercise predicts worsening of symptomatology of depression [9].

Increased age is one of the factors significantly different in the subgroup with impaired exercise capacity and this is recognized as a limiting factor in general population. Central mechanisms involving cardiovascular (arterial stiffening, increased pulse pressure, decreased endothelium-mediated vasodilatation, increased left ventricular wall rigidity, prolonged myocardial contraction, prolonged early diastolic filling rate, decreased conduction times, sclerosis and calcification of the valves, autonomic nervous system changes) [10] and respiratory system [11] along with peripheral changes (sarcopenia) [12] represent a part of the background mechanisms decreasing effort capacity in elderly.

Surprisingly, the smoker status also did not correlate with decreasing of effort capacity probably due to small number of smoker (10 patients). In one study designed on 42 smokers and 50 non-smokers, the authors have shown a greater rate-pressure product during exercise in smokers (due to significantly higher systolic blood pressure), a higher sub-maximal heart rate and finally, an impaired exercise tolerance and significantly

shorter maximal exercise test duration [13].

The exercise performance did not correlated with other cardiovascular risk factors, even if for dyslipidemia the statistical significance was at the border ($p=0.06$). The number of the patients could explain again the result. Hypertension, a well-known contributing factor to left ventricular hypertrophy, increased arterial rigidity and through these, to decreasing of physical performance, was not taken into account, because it was present in all patients except one [14].

Another unexpected result was the lack of correlation between decreased effort tolerance and the disease duration. The history of diabetes is well-known to correlate with decreasing quality of life through the increasing risk of diabetes complications. All of these complications correlate also with exercise capabilities. Janevic et al have shown that diabetes patients with complications (microvascular or cardiovascular) are less likely to reach the recommended physical activity levels compared to those without complications [15]. These patients require additional support to perform the recommended levels of physical activity. In our study the heterogeneity of the group in terms of diabetes treatment and the reduced prevalence of complication may influence this contradictory finding. The hypothesis is supported by the absence of correlation between diabetic neuropathy and poor effort tolerance among our group.

Left ventricle ejection fraction was also normal in all subjects and did not influence their effort capacity. The double product (systolic blood pressure multiplied

by heart rate) was above 22 000 W·s/min and could suggest a good mechanical work of the heart. The double product was however decreased among patients with decreased effort capacity and this supports the involvement of cardiovascular system at least in part to the decreasing of exercise capacity. Diastolic dysfunction was registered in 63.3 % of patients and represented an important determinant of limiting exercise performance. The observation converge with the results of Bajraktari et al in a study conducted in 200 patients where diastolic dysfunction was found in 68% of the diabetic patients [16]. The mechanism of diastolic dysfunction among diabetes, even if extensively studied, is not yet completely known; Early or accelerated changes into extracellular matrix, interstitial fibrosis or autonomic system involvement could result in the onset of diastolic dysfunction. As a result, asymptomatic patients at rest may be symptomatic with exercise and this further may decrease the duration of “free of symptoms” exercise which limit the patient’s daily activities and his quality of life

The multivariate regression analysis for effort capacity determinants has however shown the sedentary status overweighs the diastolic dysfunction in determination the effort intolerance. Moreover, the diastolic dysfunction was similar among sedentary and active patients even if sedentary patients have a significantly lower exercise performance.

The sedentary behavior in diabetes is a common issue [17] and factors contributing to sedentary lifestyle are many [18]; their control was demonstrated to improve the quality of live and the outcome of these patients [19]. Furthermore, these benefits could be enhanced y physical training. According to current literature, endurance training consisting of moderate – to vigorous intensity aerobic exercise (e.g., walking, cycling, etc.), 30-60 min duration, 5 days/week [20] or 150 min/week, be performed with 50–70% of maximum heart rate [21],

is expected to improve glycemic control [22], not only mediated by weight loss but also by increase in muscle sensitivity; physical training also demonstrated a better control of lipidic profile, hemodynamic parameters - diastolic performance, stroke volume, exercise blood pressure by improvement of endothelium mediated vasodilatation - and beneficial effect on cognition and on depression symptoms.

Study limitations. Given the retrospective character of our research, it is possible that some information to miss despite efforts to record all useful information. The limited dimensions of study group could lead for some of the results not to reach the statistical significance. The using of cycle-ergometer to perform exercise testing is less accurate than treadmill in terms of assessing the effort capacity neglecting the weight of the subject; this was however taken into account by testing software when calculated the effort capacity. Finally, the sedentary status of the patient was established by a self –assessment and this may have introduced bias. However the exact mentioning of time spent for certain physical activities warranted us to collect as homogenous data as possible.

In conclusion, the exercise capacity is moderate to severe decreased in at least one third of diabetic patients without overt cardiac disease and this is mainly due to their sedentary status and to diastolic dysfunction of the left ventricle. The data supports the need for educational and training programs in this category, in order to improve their quality of life and prognosis.

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