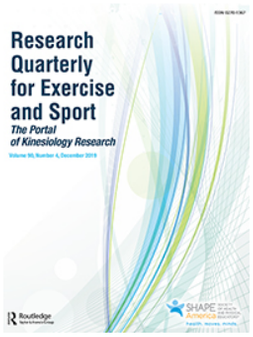

Routledge
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Research Quarterly for Exercise and Sport

ISSN: 0270-1367 (Print) 2168-3824 (Online) Journal homepage: https://www.tandfonline.com/loi/urqe20

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To cite this article: Buket Akinci, Ipek Yeldan, Selda Celik & Ilhan Satman (2019) Physical Activity Indicators, Metabolic Biomarkers, and Comorbidity in Type 2 Diabetes, Research Quarterly for Exercise and Sport, 90:4, 690-698, DOI: 10.1080/02701367.2019.1645269

To link to this article: https://doi.org/10.1080/02701367.2019.1645269

RESEARCH QUARTERLY FOR EXERCISE AND SPORT
2019, VOL. 90, NO. 4, 690–698
https://doi.org/10.1080/02701367.2019.1645269

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Physical Activity Indicators, Metabolic Biomarkers, and Comorbidity in Type 2 Diabetes

Buket Akinci [a], Ipek Yeldan[b], Selda Celik[c], and Ilhan Satman[d,e]

[a]Biruni University; [b]Istanbul University–Cerrahpasa; [c]Saglik Bilimleri University; [d]Istanbul University–Istanbul Medical Faculty; [e]Health Institutes of Turkey

ABSTRACT

Purpose: This study aimed *(1)* to compare physical activity (PA) indicators, metabolic biomarkers, and comorbidity, *(2)* to investigate the relationship between PA indicators and metabolic biomarkers, comorbidity and *(3)* to identify barriers to PA in patients with type 2 diabetes (T2DM) who are using oral hypoglycaemic agent (OHA) or combined OHA and insulin (OHAiN). **Methods:** Sixty-one patients were classified as patients using only OHA or combined OHAiN. Metabolic biomarkers (waist-to-hip ratio, body mass index (BMI), lipid profile, glycosylated haemoglobin (HbA1c), fasting blood glucose, comorbidity and PA indicators (self-reported PA, number of steps (NOS), 6-minute walking distance (6MWD)) were assessed. PA perceptions and reasons for inactivity were questioned. **Results:** The comorbidity (p = .013), low-density lipoprotein-cholesterol (p = .026), total cholesterol (p = .008) and HbA1c (p = .020) were higher and PA level was lower (p = .007) in the OHAiN group. NOS was positively correlated with high-density lipoprotein-cholesterol (p = .037) and negatively correlated with BMI (p = .007). 6MWD was negatively correlated with BMI (p = .014) and comorbidity (p = .004) in the OHA group. BMI was a significant predictor of NOS (adjusted R^2 = 0.242) and comorbidity for 6MWD (adjusted R^2 = 0.250) in the OHA group. The majority of the patients (OHA = 34.3%, OHAiN = 42.3%) reported "lack of time" as the most common barrier to PA. **Conclusions:** This study showed that patients on OHAiN have lower PA levels, poorer metabolic profiles, and higher comorbidity rates than OHA users. PA indicators were related with some metabolic biomarkers and comorbidity in only OHA users. The most common reason for inactivity was "the lack of time" in both groups.

ARTICLE HISTORY
Received 18 December 2018
Accepted 15 July 2019

KEYWORDS
Type 2 diabetes; physical activity; metabolic biomarkers; insulin therapy

Type 2 diabetes mellitus (T2DM) is a major metabolic disorder characterized by insulin resistance and impairment of β-cell function (Stumvoll, Goldstein, & van Haeften, 2005). The high prevalence of T2DM arises from unhealthy lifestyle behaviors that can cause cardiovascular comorbidities (Benjamin et al., 2017; Fox et al., 2015). Where insufficient antidiabetic medication use or the maintenance of unhealthy lifestyle behavior results in poor glycaemic control, insulin therapy may be required. In the management of T2DM, lifestyle behavior changes such as medical nutrition therapy, physical activity (PA), and exercise are low-cost treatment options, recommended by clinicians for good glycaemic control and less need for oral hypoglycaemic agents (OHA) and insulin therapy (Group, 2009; Stephenson, Smiles, & Hawley, 2014). It is well established that regular PA improves glycaemic control, reduces free fatty acid levels and helps in the prevention of cardiovascular comorbidities in patients with T2DM (Eaton & Eaton, 2017; Eckel, Grundy, & Zimmet, 2005). However, most patients retain sedentary lifestyles, as measured with PA questionnaires, pedometers and accelerometers (Healy, Winkler, Brakenridge, Reeves, & Eakin, 2015; Yates et al., 2013).

It has been reported that increased sedentary time is associated with a poorer cardiometabolic profile (Cooper et al., 2012; Fritschi & Quinn, 2010; Lim & Taylor, 2005; Loprinzi & Pariser, 2013). The biomarkers use were body mass index (BMI), waist circumference, waist-to-hip ration (WHR), high-density lipoprotein-cholesterol (HDL-chol), low-density lipoprotein cholesterol (LDL-chol), triglycerides, glycosylated hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels. In the literature, PA levels and their relationship with metabolic biomarkers are not investigated in a comparative design in T2DM patients using OHA or combined OHA and insulin (OHAiN).

T2DM is not only associated with cardiovascular comorbidities but also causes musculoskeletal comorbidities such as impaired physical capacity, weaker muscles, pain, and fatigue, which are related with inactive lifestyles

CONTACT Buket Akinci barbuket@hotmail.com Faculty of Health Sciences Division of Physiotherapy and Rehabilitation, Biruni University, 10. Yıl Caddesi Protokol Yolu. No: 45, Topkapı/Istanbul 34010, Turkey.

(Fritschi & Quinn, 2010; Gusso et al., 2008; Pantalone et al., 2015; Park et al., 2006; Sayer et al., 2005). It has been found that longer-duration of diabetes and poor glycaemic control are also associated with physical disability (Park et al., 2006). In a vicious circle, such complaints may preclude patients from participation in PA, and less PA aggravates musculoskeletal comorbidities. Additionally, personal factors such as lack of time, financial limitations or fear of hypoglycaemia are commonly perceived barriers to PA in patients with T2DM (Lidegaard, Schwennesen, Willaing, & Færch, 2016). It is unknown whether or not the perceived barriers against to PA are same both in patients using OHA and combined OHAiN.

The hypothesis of this study was that patients using insulin therapy may have lower PA levels due to musculoskeletal barriers or deconditioning, and this may be related with a high rate of comorbidity and poor metabolic profile. The study was planned to compare PA indicators, metabolic biomarkers, and comorbidity and to investigate the relationship between PA indicators, metabolic biomarkers, and comorbidity in patients using OHA or OHAiN in T2DM. Also, we aimed to subjectively identify PA perception and reasons for inactivity in patients in these groups.

Materials and methods

Study design, patients and procedures

Patients in the study were recruited from Istanbul University Medical Faculty Diabetes Outpatient Clinic from April to October 2017. Ninety-two patients diagnosed with T2DM for at least one year, aged 35–65 years, with HbA1c levels between 7 and 11%, measured in the last month, were screened. Exclusion criteria were as follows; use of only insulin therapy, medium or low adherence to OHA or insulin therapy (Morisky Medication Adherence Scale score <8) (Morisky, Green, & Levine, 1986), diagnosis of severe pulmonary disease, malignant disorders, uncontrolled heart failure, severe musculoskeletal disorder, neuropathy, neuropathic pain, amputation, venous insufficiency, pregnancy, breastfeeding, and insufficient cooperation. Informed consent was obtained from all patients. The study protocol was approved by the Ethical Committee (No: 2017/6–1). The study was conducted in accordance with the principles of the Helsinki Declaration.

Patients were divided into two groups according to insulin use. Patients in the OHA group (n = 35) were using only OHA, and patients in the OHAiN group (n = 26) were using combined OHA and insulin. The mean age of the OHA and OHAiN groups were 51.4 ± 7.1 and 53.5 ± 6.0 years, respectively. The use of medication and insulin prescribed by the physician was allowed for the patients during the study period.

Measures

Physical activity

Sociodemographic and clinical features of the patients were recorded. Self-reported PA was obtained for the last 7 days; a short, self-administered version of the International Physical Activity Questionnaire-Short Form (IPAQ) (Craig et al., 2003). Data from the questionnaire were summed within each item (i.e. vigorous intensity, moderate intensity, walking) to estimate the total amount of time spent in PA per week (Saglam et al., 2010). For the objective assessment of PA level, step count was also recorded by a pedometer (Omron HJ 321E Walking Style). Patients' weight, height, and step length data were entered into the device. Patients wore a pedometer on the belt for seven consecutive days after the examination, except when sleeping, while patients continued with their daily routines. The device calculated the mean number of steps (NOS) for seven days.

All of the subjects performed a 6-minute walking test (6MWT) to determine their functional exercise capacity. The 6MWT was performed according to the American Thoracic Society statement, in a 30 m corridor (Enright, 2003). Before and after the test; oxygen saturation, heart rate, and systolic and diastolic blood pressures were recorded, and total walking distance (6MWD) was noted.

Metabolic biomarkers

Metabolic biomarkers (consecutively; HbA1c, FBG, total cholesterol, HDL-chol, LDL-chol, and triglycerides) were derived from the medical records of the same university laboratory in the final month.

Anthropometric parameters

The height, weight, waist circumference and hip circumference were directly measured. For the determination of WHR, waist circumference at the umbilical level was measured in the late exhalation phase while standing and hip circumference at the trochanter major of femur level. BMI and WHR were calculated.

Comorbidity

The comorbidity score was calculated with the Charlson Comorbidity Index (CCI) which contains 19 comorbidity categories, which are primarily defined using International Classification of Diseases-

9-Clinical Modification diagnosis codes excluding diabetes (Charlson, Pompei, Ales, & MacKenzie, 1987). Three comorbidity levels were defined as; low (score of 0), medium (score of 1–2), and high (score of 3+). The total CCI scores range from 0 to 37. The overall comorbidity score reflects the cumulatively increased likelihood of 1-year mortality.

Physical activity perception

The PA perception of the patients was subjectively asked with a short survey containing two questions (Figure 1). Question 1 of the survey asked whether levels of PA were adequate for good glycaemic control. If the answer was "No," possible reasons for inactivity were sought in question 2. The questions and reasons were refined according to previous studies by the researchers (Chang et al., 2018; Lidegaard et al., 2016). Reasons were listed as; R1. "*I have no reason for being physically inactive,*" R2. "*I have no spare time for physical activity,*" R3. "*My financial resources are not enough for physical activity,*" R4. "*There is no local area for physical activity,*" R5. "*I feel pain/stiffness/fatigue/dyspnea with physical activity,*" R6. "*I experience hypoglycaemia with physical activity,*" R7. "*I don't think that physical activity is effective for good glycaemic control.*" Patients were allowed to choose more than one reason.

Assessments were performed by the same physiotherapist and nurse. The PA perception survey and IPAQ were completed under supervision on the same day of the week; one assessment session lasted approximately 30 minutes.

Statistical analysis

Statistical analysis data were evaluated using the Statistical Package for Social Science (SPSS) 20.0 program for Windows and by analyzing descriptive statistics (frequency, mean, and standard deviation). The Kolmogorov–Smirnov test was used to establish the normal distribution of data. Patients' demographic and clinical features were compared with an Independent sample t-test for parametric variables, Mann Whitney-U test for nonparametric variables and chi-square test used for the percentages. Intercorrelations among parameters were computed using Pearson's correlation analysis. A correlation coefficient (r) between 0.26 and 0.49 reflects poor agreement, those between 0.50 and 0.69 reflect moderate agreement, and those ≥0.70 reflect high agreement. A multiple linear regression analysis was performed to determine the multivariate influence of the predictors of PA indicators. The independent variables were included in the model based on the results of the univariate analysis. The adjusted R^2 was used to explain the total variance. A p value <.05 was considered statistically significant for all tests.

Results

A total of 92 patients with T2DM were assessed in terms of eligibility in the study. Thirty-one patients were not included for the following reasons; showing medium or low adherence to OHA or insulin (n = 11), using only insulin (n = 4), having severe musculoskeletal disorders (n = 4), pregnancy (n = 1), unwillingness to participate in the assessment session (n = 9). Sixty-one patients (43 female, 18 male) were enrolled in the study. Thirty-six patients in the OHA group and 25 patients in the OHAiN group completed the study and were included in the statistical analysis.

The characteristics and comparison of the groups

Thirteen patients (37.1%) in the OHA group and 8 patients (30.8%) in the OHAiN group were overweight (BMI = 25–29.99 kg/m^2). Twenty-one patients (60%) in the OHA group and 16 patients (61.5%) in the OHAiN group were obese (BMI ≥30 kg/m^2). Eighteen patients (51.4%) in the OHA group and 16 patients (61.5%) in the OHAiN group were insufficiently active (IPAQ

Question 1. Do you think that your physical activity level is enough for good glycaemic control?
□ Yes □ No
If the answer is "No",
Question 2. What is the reason?
Reason 1. I have no reason for being physically inactive
Reason 2. I have no spare time for physical activity
Reason 3. My financial resources are not enough for physical activity
Reason 4. There is no local area for physical activity
Reason 5. I feel pain/stiffness/fatigue/dyspnea with physical activity
Reason 6. I experience hypoglycaemia with physical activity
Reason 7. I don't think that physical activity is effective for good glycaemic control

Figure 1. Physical activity survey.

<600 MET). None of the patients was active (IPAQ ≥3000 MET) in both groups.

Comparison of OHA and OHAiN groups showed that the duration of diabetes ($p < .0001$, 95% CI: −9.9, −3.8), comorbidity severity ($p = .013$, 95% CI: −1.73, −0.20), PA levels ($p = .007$, 95% CI: 95.21, 562.50) LDL-chol ($p = .026$, 95% CI: −36.83, −2.45), total cholesterol ($p = .008$, 95% CI: −41.47, −6.4), and HbA1c ($p = .020$, 95% CI: −1.52, −0.13) were significantly higher in the OHAiN group than in the OHA group. Biguanide (BG; metformin) and sulphonylureas (SU) were more commonly used in the OHA than in the OHAiN group ($p = .003$, and $p < .0001$, respectively). The other characteristics or clinical parameters did not show significant differences between the two groups ($p > .05$) (Tables 1 and 2).

The comparison of the groups by gender were not significant for weight (consecutively for female and male; $p = .451$, $p = .487$), BMI ($p = .765$, $p = .737$) and WHR ($p = .308$, $p = .273$) (Table 1).

The relationship between physical activity indicators and metabolic biomarkers, and comorbidity and results of multiple regression analysis

The NOS was positively correlated with the duration of diabetes ($p = .02$, $r = 0.399$) and HDL-chol ($p = .037$, $r = 0.364$) and negatively correlated with BMI ($p = .007$, $r = −0.453$). 6MWD negatively correlated with BMI ($p = .014$, $r = −0.413$) and comorbidity ($p = .004$, $r = −0.480$) in the OHA group (Table 3). Two separate multiple linear regression model was conducted to determine the predictors of NOS and 6MWD as dependent variables in the OHA group. The results from the first model, where NOS was the dependent variable and duration of diabetes, HDL-chol and BMI were independent variables revealed significant regression for BMI (F (3.29) = 4.405 $p = .01$). The BMI was the only significant predictor of NOS accounting for 24% of the variance (ß = −0.349, $p = .045$). In the second model, 6MWD was the dependent variable and CCI and BMI were independent variables (F (2.32) = 6.674, $p = .004$). The CCI was the only significant contributor to 25.2% of the variance explained in the significant regression for 6MWD (ß = −0.381, $p = .023$) (Table 4).

The relationship between PA indicators and time to onset of insulin treatment, insulin dose, glycaemic control, metabolic biomarkers, and comorbidity for the OHAiN group are presented in Table 5. There was no correlation between PA indicators, comorbidity, and metabolic biomarkers.

Table 1. The demographic and clinical characteristics of the groups.

	Mean±SD or n (%)		
	OHA ($n = 35$)	OHAiN ($n = 26$)	p value
Age (year)	51.4 ± 7.1	53.5 ± 6.0	.222
Gender			
Female	26 (74.3%)	17 (65.4%)	.455
Male	9 (25.7%)	9 (34.6%)	
Working status			
Non-worker	11 (31.4%)	6 (23.0%)	.535
Retired	10 (28.6%)	10 (38.5%)	
Active worker	14 (40.0%)	10 (38.5%)	
Duration of diabetes (year)	7.9 ± 5.7	14.8 ± 5.9	**<.0001**
Type of OHA			
BG (metformin)	35 (100%)	20 (76.9%)	**.003**
SU (gliclazide/glimepiride)	16 (45.7%)	-	**<.0001**
GLIN (repaglinide)	3 (8.6%)	7 (26.9%)	.056
DPP-4i (vilda/sita/saxagliptin)	14 (40.1%)	9 (34.5%)	.668
TZD (pioglitazone)	1 (2.9%)	1 (3.8%)	.830
Time to onset of OHA treatment (year)	7.97 ± 5	14.9 ± 5.9	**<.0001**
Type of insulin			
Basal (glargine/detemir)	-	14 (53.8%)	-
Prandial (HM regular/aspart/lispro)	-	4 (15.3%)	-
Basal+prandiyal		8 (30.7%)	
Time to onset of insulin treatment (year)	-	6.0 ± 5.4	-
Dose of insulin (IU per day)	-	48.9 ± 23.0	-
Charlson Comorbidity Index (0–37)	1.91 ± 1.33	2.88 ± 1.63	**.013**
Weight (kg)			
Female	83.3 ± 16.0	79.6 ± 15.7	.451
Male	95.8 ± 13.2	90.3 ± 139	.487
BMI (kg/m^2)			
Female	32.9 ± 5.7	32.3 ± 6.5	.765
Male	31.1 ± 3.3	30.9 ± 3.8	.737
WHR			
Female	0.95 ± 0.06	0.97 ± 0.04	.308
Male	0.97 ± 0.03	1.02 ± 0.06	.273

Note. SD, standard deviation; OHA, oral hypoglycemic agent; OHAiN, oral hypoglycemic agent and insulin, BMI, body mass index; WHR, waist-to-hip ratio; BG, biguanides; SU, sulphonylureas, GLIN, glinides; DPP-4i, dipeptidyl peptidase-4 inhibitors); TZD, thiazolidinediones; HM, human insulin; IU, international unit.

Physical activity perceptions and barriers to physical activity

The responses of the PA perception survey of the patients are shown in Figure 2. Sixty-eight percent of the patients thought that their PA level was insufficient for good glycaemic control in the OHA group and 88.5% thought so in the OHAiN group. The most common barriers to PA were noted respectively: R2 (34.3%), R4 = R5 (31.4%), R1 = R3 (11.4%), R6 (2.9%) in the OHA group and R2 (42.3%), R5 = R6 (30.8%), R4 (23.1%), R1 (15.4%), R3 (3.8%) in the OHAiN group. In both groups, R2 (no spare time for PA) was the most important barrier to PA.

Post-hoc power analysis

At the end of the study, the achieved power of the study was computed by "G*Power (3.1.9.2) Sample Size Calculator" according to the mean IPAQ scores of the groups (OHA = 839.28 ± 568.7, OHAiN = 510.42 ± 336.9). The

Table 2. Demographic and clinical characteristics of the groups.

	Mean±SD or n (%)		
	OHA (n = 35)	OHAiN (n = 26)	p value
HbA1c, % (mmol/mol)	7.84 ± 1.08 (62 ± 2.2)	8.67 ± 1.49 (71 ± 2.3)	**.020**
Optimal controlled (HbA1c ≤7.0%)	12 (34.3%)	2 (7.7%)	
Moderately controlled (HbA1c 7.1–9.0%)	20 (57.1%)	15 (57.7%)	
Uncontrolled (HbA1c ≥9.0%)	3 (8.5%)	9 (34.6%)	
FBG (mg/dL)	167.5 ± 48.9	197.6 ± 77.5	.090
HDL-chol (mg/dL)	47.7 ± 10.8	48.9 ± 11.4	.673
LDL-chol (mg/dL)	117.7 ± 31.7	137.4 ± 32.7	**.026**
Triglycerides (mg/dL)	182.5 ± 109.4	177.8 ± 103.4	.871
Total cholesterol (mg/dL)	197.2 ± 34.6	221.2 ± 32.0	**.008**
NOS	6141 ± 1946	5796 ± 2240	.526
IPAQ (MET)	839.3 ± 568.7	510.4 ± 336.9	**.007**
6MWD (m)	498.2 ± 62.1	481.4 ± 41.5	.239
Resting SBP (mmHg)	121 ± 22	128 ± 17	.199
Resting DBP (mmHg)	77 ± 10	79 ± 9	.485
Resting HR (per minute)	83 ± 12	86 ± 10	.475

Note. OHA, oral hypoglycemic agent; OHAiN, oral hypoglycemic agent and insülin; SD, standard deviation; HbA1c, glycosylated hemoglobin A1c; FBG, fasting blood glucose; HDL-chol, high-density lipoprotein-cholesterol; LDL-chol, low-density lipoprotein-cholesterol; NOS, number of steps; IPAQ, International Physical Activity Questionnaire; 6MWD, 6-minute walking distance; MET, metabolic equivalent, SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 3. The correlation analysis between physical activity indicators and metabolic biomarkers and comorbidity in OHA group.

	Duration of diabetes (yr) r	BMI (kg/m^2) r	WHR r	CCI (0–37) r	HbA1c (%) r	FBG (mg/dL) r	HDL-chol (mg/dL) r	LDL-chol (mg/dL) r	Total cholesterol (mg/dL) r	IPAQ (MET/wk) r	NOS r
IPAQ (MET/wk)	−0.164	−0.163	−0.044	−0.246	0.076	−0.135	−0.064	0.177	−0.046		
NOS	**0.399***	**−0.453****	−0.267	−0.021	0.013	0.138	**0.364***	0.017	−0.057	0.159	
6MWD (m)	−0.042	**−0.413***	0.023	**−0.480****	0.250	0.162	0.173	−0.062	0.096	0.015	0.267

Note. yr, year;B MI, body mass index;WHR, waist-to-hip ratio; CCI, Charlson Comorbidity Index; HbA1c, glycosylated hemoglobin A1c; FBG, fasting blood glucose; HDL-chol, high-density lipoprotein-cholesterol; LDL-chol, low-density lipoprotein-cholesterol; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; wk, week; 6MWD: 6-Minute walking distance; NOS, number of steps.
*p < .05; **p < .01 Pearson correlation test.

Table 4. Multiple regression analysis for OHA group.

Dependent variables	Independent variables	B	Standart Error $_B$	β	t	p	95% CI	Adjusted R^2	p
Number of steps	Duration of diabetes (year)	60.038	60.172	0.179	0.998	.327	−63.02/183.1	0.242	.011
	BMI (kg/m^2)	−144.529	68.983	−0.349	−2.095	**.045**	−285.61/-3.44		
	HDL-chol (mg/dL)	40.621	31.165	0.221	1.303	.203	−23.12/104.36		
6 MWD (m)	BMI (kg/m^2)	−3.222	1.886	−0.272	−1.708	.097	−7.06/0.62	0.250	.004
	CCI (0–37)	−17.709	7.401	−0.381	−2.393	**.023**	−32.78/-2.63		

Note. BMI, body mass index; CCI, Charlson Comorbidity Index; HDL-chol, high-density lipoprotein-cholesterol; 6MWD: 6-Minute walking distance; NOS, number of steps.

Table 5. The correlations between physical activity indicators and insulin usage regime, metabolic biomarkers and comorbidity for OHAiN group.

	TOI (yr) r	ID (unit) r	Duration of diabetes (yr) r	BMI (kg/m^2) r	WHR r	CCI (0–37) r	HbA1c (%) r	FBG (mg/dL) r	HDL-chol (mg/dL) r	LDL-chol (mg/dL) r	Total cholestherol (mg/dL) r	IPAQ (MET/wk) r	NOS r
IPAQ (MET/wk)	−0.232	−0.081	−0.362	0.335	−0.014	0.060	0.234	0.206	−0.010	0.303	0.071		
NOS	−0.181	−0.057	−0.124	−0.170	−0.263	−0.040	−0.188	−0.187	−0.372	0.329	0.247	0.286	
6MWD (m)	−0.064	−0.368	−0.198	−0.380	0.054	−0.372	−0.057	−0.183	0.406	−0.252	−0.288	−0.260	0.311

Note. yr, year; TOI, time to onset of insulin; ID, insulin dose; BMI, body mass index; WHR, waist-to-hip ratio; CCI, Charlson Comorbidity Index; HbA1c, glycosylated hemoglobin A1c; FBG, fasting blood glucose; HDL-chol, high-density lipoprotein-cholesterol; LDL-chol, low-density lipoprotein-cholesterol; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; wk, week; 6MWD, 6-Minute walking distance; NOS, number of steps.

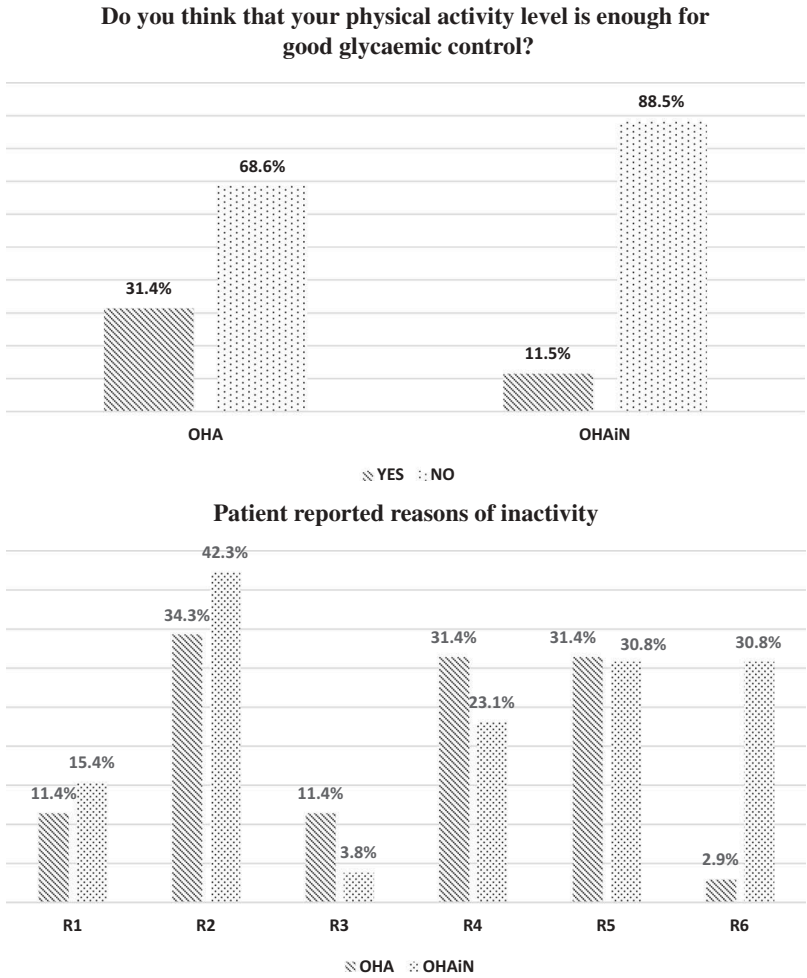

Figure 2. Physical activity perceptions and reasons for inactivity of the patients. *Note*. R1. I have no reason for being physically inactive, R2. I have no spare time for physical activity, R3. My financial resources are not enough for physical activity, R4. There is no local area for physical activity, R5. I feel pain/stiffness/fatigue/dyspnea with physical activity, R6. I experience hypoglycaemia with physical activity, none of the patients reported R7.

achieved power of the study was 85% ($\alpha = 0.05$, effect size $d = 0.70$).

Discussions

The results of this study have shown that patients using combined OHAiN have lower PA levels, poorer metabolic profiles and higher comorbidity rates than patients using only OHA. While NOS and functional exercise capacity were related with comorbidity or some metabolic biomarkers in the OHA group, PA indicators were not related with comorbidity or metabolic biomarkers in the OHAiN group. The BMI was a significant predictor of NOS and comorbidity for 6MWD in OHA group. In addition, a high percentage of the patients believed that their PA level was insufficient for good glycaemic control and the most common reason for inactivity in both groups was the lack of time for PA. The distinctive barrier to PA was "experience of hypoglycaemia" in the OHAiN group. In this study, we preferred to include patients with a wide spectrum of glycemic control (HbA1c 7–11%). Thus, it was possible to learn about the PA profile of the patients with good and bad glycemic control.

In the study, PA level was assessed both objectively and subjectively. As predicted, patients in the OHAiN group were less physically active than those in the OHA group, according to IPAQ. It seems that rather than age, but the long duration of T2DM makes the self-management of the disease difficult, even though patients know the benefits to disease control of healthy lifestyle behavior. The mean NOS was found to be lower than the recommended level (8000–10,000 step per day) (Colberg et al., 2010) in both the OHA (6141.35 ± 1946.26) and OHAiN (5796.34 ± 2239.81) groups. It has been reported that use of pedometer improves some biological biomarkers, such as blood

pressure and lipid profile but there is inconsistent evidence about its effects on glycaemic control (Qiu et al., 2014; Shenoy, Guglani, & Sandhu, 2010). The relationship between glycaemic control and NOS remains unclear in both groups in our study. Although NOS was found to be related with some metabolic biomarkers in the OHA group (BMI, HDL-chol), this study failed to demonstrate any relationship between PA indicators and comorbidity, and the biological markers in the OHAiN group. Similar to the previous findings of Yates et al. (Yates et al., 2013), we did not find any relationship between metabolic biomarkers and self-reported PA levels. This difference may arise from the diversity of the assessment methods. While pedometers focus solely on walking, IPAQ investigates multidimensional PA and walking is taken into account only if it lasts at least 10 minutes.

An unexpected result was that a positive correlation between duration of diabetes and the NOS was found in the OHA group. This result may support the fact that over the years, patients in this group were able to manage T2DM with a combination of OHA and PA.

The 6MWT may be influenced by some musculoskeletal complaints, such as pain or fatigue in the lower extremity. In this study, the 6MWT was used as a PA indicator. Stewart et al. (Stewart et al., 2016) found that 6MWD of the patients with T2DM was significantly lower than in healthy subjects, and the authors explained this finding through early cardiovascular disease or deconditioning. The factors leading to decreased functional exercise capacity can also limit PA levels. Patients in the current study showed better functional exercise capacity (mean 6MWD of the total = 491.03 ± 77.7 m) compared with previous studies (Ingle, Reddy, Clark, & Cleland, 2006; Nielsen et al., 2016; Stewart et al., 2016). Latiri et al. (Latiri et al., 2012) studied 6MWD in patients with T2DM without insulin therapy and they found higher mean 6MWD (566 ± 81 m) than the OHA group in this study (498.17 ± 62.1). This discrepancy may originate from the difference in PA levels of the study populations. Additionally, in our study, regression analysis revealed that comorbidity was predictor of 6MWD in the OHA group. Stewart et al. (Stewart et al., 2016) recommended frequent measurement of 6MWT for comprehensive strategies for treating T2DM. Our results confirm that this test may be sensitive in the detection of functional impairments due to comorbidities in T2DM patients without insulin therapy.

Central obesity was found to be associated with diabetes and three obesity indicators, BMI, waist circumference and WHR, are strong and consistent predictors of T2DM (Qiao & Nyamdorj, 2010). Qiao et al. (Qiao & Nyamdorj, 2010) stated that waist circumference or WHR discriminate better in diabetes patients than in those without diabetes, as compared with BMI. We did not observe differences in any anthropometric parameter in the comparison of the groups based on gender. In our study, the regression analysis showed that BMI has an impact on NOS in the OHA group. This result may confirm Qui et al. (2014) who were reported that walking is associated with a reduction in BMI. Unlike the studies of Qiao & Nyamdorj (2010) and Qiu et al. (2014), HDL-chol was found to be correlated with the increased NOS in the OHA group in the present study.

In this study, the dosage of the medications (OHA and/or insulin) were adjusted according to the patient's requirements on an individual basis as suggested in our national (Satman et al., 2017) and international guidelines as well (American Diabetes Association, 2017). The basic treatment is metformin and healthy lifestyle modifications. Metformin is the first option in the treatment of T2DM in the word, because it is less expensive, the risk of hypoglycaemia is low and it does not lead to weight gain. When metformin is not sufficient for glycaemic control, other types of OHA or insulin is added to the treatment. It has been found that patients on insulin therapy have more comorbidities arising from the long duration of diabetes. Increased insulin requirement was also related to high HbA1c, FBG, and comorbidities, but we were unable to confirm our hypothesis that PA indicators are related to metabolic biomarkers and comorbidities in patients on combined OHAiN therapy. The complexity of the disease's characteristics, the small sample size and other factors, such as dietary habits, muscle strength and the psychologic status of the patients, might be responsible for this unclear picture in patients on insulin therapy.

The patients in the OHAiN group were more aware that their PA level was insufficient for good glycaemic control. Thomas, Alder, and Leese (2004) reported that the lack of local area and cost of exercise were the most common reasons of inactivity in people with diabetes in the United Kingdom. Lidegaard et al. (2016) investigated the barriers to PA with a longer survey in patients with T2DM in Denmark. They outlined the lack of local space or knowledge about exercise and the cost of training programs as the most common reasons for inactivity. Chang et al. (2018) also noted similar perceived barriers to PA in low-income Latino women at risk for T2DM. Unlike the previous findings, a common reason for inactivity in both groups was "lack of time for PA" in the present study. The different outcomes from the previous studies may arise from the sociocultural differences of the study populations. Secondly, both groups reported that

they feel pain/fatigue/stiffness or dyspnea with PA. These complaints may be related to musculoskeletal comorbidities, decreased functional exercise capacity and deconditioning. In this study, 30.8% of patients on insulin therapy experienced hypoglycaemia with PA. These patients must be trained how to avoid hypoglycaemia during PA.

The study has some limitations. Our study population was relatively small because of the rigorous selection of the patients with high adherence to OHA and insulin and the exclusion of severe comorbidities, which can limit assessments. The study was conducted in a single tertiary local center. Although PA perception survey was a subjective survey which was created based on previous studies, however, perceived barriers may vary in different cultures. The results of the small and women majority sample size cannot be generalized to the whole T2DM population. Also, factors related to metabolic biomarkers, such as dietary habits, psychological condition, sitting time and sleep duration were not assessed in the study. We believed that further studies are needed to investigate the effect of psychologic factors on PA levels in a large population, considering insulin type in patients with T2DM.

Conclusion

This comparative study showed that patients using combined OHAiN were less active and had poorer metabolic profiles and comorbidities compared with users of OHA alone. Some of the PA indicators were related with metabolic biomarkers and comorbidity in patients using OHA. Additionally, BMI was a significant predictor of NOS and comorbidity for 6MWD in patients using OHA. However, in contrast to our hypothesis, this result is not verified for patients on combined OHAiN. A high percentage of the patients believed that their PA level was insufficient for good glycaemic control and the most common reason for inactivity in both groups was "lack of time for PA." The distinctive barrier to PA was "experience of hypoglycaemia" in the patients using combined OHAiN.

What does this article add?

To the best of our knowledge, this is the first study compared the PA indicators, including functional exercise capacity, metabolic biomarkers, and comorbidity in T2DM patients using OHA only or combined OHAiN. In addition, the relationship between PA indicators and metabolic biomarkers and reasons for inactivity were investigated in each group. This study adds to the literature that patients who are using OHA or the combination of OHAiN showed differences in terms of PA levels, comorbidity, metabolic profile and the relationships between these parameters. Also, patients using OHA or combined OHAiN presented diverse PA levels and some reasons for inactivity. It seems that if the medical treatment can be supported with PA in T2DM patients on OHA only, this may have an impact on some metabolic biomarkers and comorbidity. Therefore, these differences should be taken into account and specified goals for PA should be determined in T2DM patients using OHA or combined OHAiN.

ORCID

Buket Akinci http://orcid.org/0000-0002-9878-256X

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