Long-term Physical Activity Decreased the Risk of New-onset Hypertension in Type 2 Diabetes Mellitus Patients with Pre-hypertension: A Retrospective Cohort Study

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Article

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Abstract

Background Numerous studies were demonstrated the inverse relationship between all kinds of physical activity (PA) and cardiovascular diseases (CVDs), few of them focus on the new-onset hypertension. Therefore, this study was aimed to determine the impact of long-term PA on the risk of new-onset hypertension in type 2 diabetes mellitus (T2DM) patients with pre-hypertension.

Methods A total of 268 T2DM patients with pre-hypertension were recruited between January and December 2015, and followed them up until December 2020. All patients were took PA self-assessment. Demographic, clinical, laboratory, radiologic, treatments, complications, lifestyle and clinical outcomes data were extracted from electronic medical records or collected through a structured interview.

Results During 5 year follow-up, the incidence of new-onset hypertension was significantly lower in PA group (15.5% vs 35.4%, $p<0.01$) when compared to the physical inactivity (PIA) group. Logistic regression analysis showed that PA (OR 0.337, 95%CI 0.168 to 0.677, $p<0.01$), body mass index (BMI) (OR 1.138, 95%CI 1.019 to 1.272, $p<0.05$) and glycosylated hemoglobin (HbA_{1C}) (OR 1.206, 95%CI 1.006 to 1.446, $p<0.05$) were associated to the incidence of new-onset hypertension in pre-hypertensive T2DM patients. Subgroup analysis found that for those overweight and poorly controlled pre-hypertensive T2DM patients, long-term PA were less likely to develop hypertension (overweight: OR 0.187, 95%CI 0.063 to 0.558, $p<0.01$; glycaemic glucose poor controlled: OR 0.349, 95%CI 0.138 to 0.880, $p<0.05$).

Conclusion These results suggested that long-term PA might be an important protective factor for new-onset hypertension in overweight and poor blood glycaemic controlled pre-hypertensive T2DM patients.

Background

Type 2 diabetes mellitus (T2DM) is an important global public health problem with high morbidity and disability. Due to the aging population and unhealthy lifestyles, the prevalence of diabetes tends to continue to rise. The global diabetes prevalence in 2019 was estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. Poorly controlled diabetes can mediate multiple organ damage, leading to microvascular and macrovascular complications, including kidney failure, blindness, amputation, and cardiovascular disease (CVDs) [2] [3]. Despite the medical research of diabetes was already mature and the treatment was comprehensive, T2DM remained considered as an incurable disease, and patients with T2DM still suffered high rates of complications.

Hypertension, as well as diabetes, is another one considered risk factors for CVDs and microvascular complications [4]. Unfortunately, they are frequently present together. Hypertension is twice more common in diabetics than in non-diabetics; patients with T2DM are more commonly present with isolated systolic hypertension and are more resistant to treatment. Furthermore, population co-existed with T2DM and hypertension had significantly higher risk for coronary heart disease (CHD) [5], left ventricular hypertrophy [6], congestive heart failure [7] and stroke [8] than population with either condition alone. More importantly, microvascular complications, retinopathy and nephropathy are also more common in

patient co-existed with hypertension and T2DM [9, 10]. Pre-hypertension, defined as systolic and diastolic blood pressure (SBP/DBP) 120–139/80–89 mmHg. BP in the upper half of this range was also roughly double risk for cardiovascular events, even in the absence of progression to hypertension. Globally, overall CVDs affect approximately 32.2% of all persons with T2DM and are major cause of mortality among T2DM patients, accounting for approximately half of all deaths over the past years. Therefore, among patients with T2DM, prevent hypertension and other CVDs complications are particularly beneficial.

The long-term complications of T2DM can be delayed by taking medications as prescribed along with a healthy lifestyle (i.e., diet and physical activity). Comprehensive lifestyle managements are recommended as the first-line therapy for T2DM in the current guidelines [11, 12]. Along with glycemic control, physical exercise has a number of benefits, such as decreasing insulin resistance and improving aerobic capacity, body composition, endothelial functions and cardiovascular fitness [13]. Patients living with diabetes are recommended to engage in 150 min of moderate-to-vigorous intensity aerobic activity per week to realize benefits on metabolism, fitness, and wellbeing; In addition, resistance and flexibility exercises are recommended two to three times per week [14]. A meta-analysis concluded that exercise training, including aerobic and resistance training, decreases hemoglobin A_{1c} (HbA_{1c}) by 0.66% in individuals with T2DM [15]. Another meta-analysis found that exercise was associated with an average decrease of 0.80% in HbA1c, while there was no difference in the range of HbA1c changes between aerobic training, endurance training or combined training [16]. Studies with low-volume high intensity training (HIT) in T2DM patients suggested that it can rapidly improve glucose control [17]. One meta-analysis of cohort studies coupled with results from a prospective cohort study have demonstrated an inverse relationship between physical activity (PA) and both CVDs and all-cause mortality in DM patients [18]. Of important, a randomized controlled trial showed that there was any difference between the intensive lifestyle intervention and standard diabetes education over 10 years in terms of a composite cardiovascular endpoint (consisting of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke and hospitalization for angina) [19].

Numerous studies were demonstrated the inverse relationship between all kinds of PA and CVDs in DM patients, mostly of them were meta-analysis study. However, few of them focus on the impact of long-term PA on the new-onset hypertension in T2DM patients with pre-hypertension. Therefore, this retrospective cohort study aimed to determine the relationship between long-term PA and the incidence of new-onset hypertension in T2DM patients with pre-hypertension.

Methods

Study population

This retrospective cohort study included outpatients and inpatients from January 2016 to December 2020. T2DM patients with pre-hypertension were recruited. We defined T2DM as fasting plasma glucose (FPG) ≥7.00 mmol/L or self-reported receipt of antidiabetic treatment [20]. Pre-hypertension was defined

as SBP/DBP of 120-139/80-89 mm Hg, in participants without a history of hypertension and use of antihypertensive medication [21]. The exclusion criteria were: no available information on characteristics; no available HbA_{1C} value and glucose value; participants diagnosed with hypertension or other CVDs at baseline and participants with undefined CVDs status at follow-up; visit intervals < 1 years; and lost to follow-up. Cohort entry was defined as the date of the initial visit between January and December 2016, and follows them up until December 2020.

Data collection

Clinical data (including demographic characteristics, lifestyle, medical history and family history of hypertension and CVDs) and results of laboratory test (including blood glucose, blood lipids, etc) were collected from an electronic clinical information system at baseline or collected through a structured interview.

All patients underwent biochemistry examination were performed on an auto analyzer (Beckman 5800), including fasting plasma glucose (FPG), triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), and alanine aminotransferase (ALT).

Exposure of interest

PA was evaluated by patients themselves. The evaluated standard based on the American Diabetes Association Standards for Diabetes Care 2014 : adults with diabetes should be advised to perform at least 150 minutes per week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise; In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice each week [14]. All patients were took exercise evaluation at initial visit. Subjects who did not meet the above conditions were classified as physical inactivity (PIA) group; on the contrary, as PA group.

Outcome measures and follow-up

The outcomes of interest were incident of new-onset hypertension and other CVDs complications during follow-up period. All subjects participated in physical examinations every year and they would see a doctor in our hospital if there was any discomfort. In addition, almost every surviving patient accepted follow-up for blood pressure and other examinations every 3 months for new-onset hypertension, and other CVDs from the electronic clinical information system in December of each year until 2020.

New hypertension and CVDs were recorded in all patients. Hypertension was defined as either systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported receipt of antihypertensive treatment [22]. The CVDs included femoral/carotid atherosclerosis (AS), coronary AS, cerebral ischemic focus, CHD, percutaneous coronary intervention (PCI), and coronary artery bypass graft.

Blood pressure value was obtained by trained staff using standard mercury sphygmomanometers through office blood pressure measurements. Femoral/carotid AS was diagnosed by vascular B-ultrasound. Coronary AS and CHD were diagnosed by coronary computed tomography angiography (CTA) or coronary angiography. Cerebral ischemic focus diagnosed by head computed tomography scans (CT) or nuclear magnetic resonance imaging (MRI).

Covariates

Covariates of interest included age, gender, BMI, FPG, triglycerides, total cholesterol, HDL-C, LDL-C, ALT, smoking status, drinking status, family history of hypertension. As for participants' personal habits, participants were classified by smoking status into current smokers or not. Current smoker was defined as having a current smoking habit regardless of the number of cigarettes smoked per day, and habitual drinker was defined as consuming ≥150 g of alcohol per week.

Statistical analyses

Evaluation of normality was performed with Shapiro-Wilk test. Continuous variables were expressed as the means ±standard deviations (normal distribution), and categorical variables were expressed as frequency or percentages. Independent-samples T test was used for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and chi-square tests for categorical variables. Missing continuous variables were mainly supplemented by means or median. We evaluated the unadjusted and adjusted ORs of incident hypertension using univariate and multivariate logistic regression analyses.

The ethics committee of Zhejiang Hospital approval

The study was approved by the ethics committee of Zhejiang Hospital (No. 2022-39K). The data are anonymous, and the requirement for informed consent was therefore waived by the ethics committee of Zhejiang Hospital. Correspondence and requests for data should be addressed to Q.Wu.

Statement of human right

All research procedures in this study involving human participates were performed according to the ethical standards of the Zhejiang hospital and/or national research committee and the criteria of the declaration of Helsinki (1964) and its later amendment or comparable ethical standards.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due the restrictions apply to the availability of these data, but are available from the corresponding author on reasonable request.

Results

Participants' characteristics

We identified 268 patients who met our inclusion criteria (Fig. 1). The age range of population was 36 to 76 years, the mean age were 58.15 ± 9.17 years. The study population included 208 men (77.6%) and 60 women (22.4%). Table 1 presents the characteristics of the participants. There were 110 subjects (41%) with a physical activity lifestyle and 158 (59.0%) with an inactivity lifestyle. In the PA group, the mean age was 55.89 ± 8.68 years, with a mean BMI of 24.50 ± 2.41 and the percentages of males were 78 (70.6%).

Meanwhile, compared with those in the PIA group, those with a regular physical activity lifestyle had significantly younger age. We observed that patients with regular physical activity lifestyle had significantly lower levels of Scr, uric acid, cholesterol, LDL-C, and m-Alb/Cr. We also observed that the proportion of smoking, drinking and family history of hypertension was similar in the two groups.

Table 1
Baseline characteristics of participants

	Total (N = 268)	PA group (N = 110)	PIA group (N = 158)	P value
Age (years)	58.15 ± 9.17	55.89 ± 8.68	59.77 ± 9.20	0.001**
Gender (Female n,%)	60 (22.4%)	32 (29.1%)	28 (17.7%)	0.037*
BMI (kg/m^2)	25.95 ± 12.21	24.50 ± 2.41	26.92 ± 15.74	0.113
SBP (mmHg)	126.21 ± 8.62	125.00 ± 8.697	127.04 ± 8.49	0.057
DBP (mmHg)	78.41 ± 7.91	77.68 ± 8.60	78.92 ± 7.39	0.207
Years of T2DM (n,%)				0.555
<5 years	187 (70.03%)	80 (72.7%)	108 (68.4%)	
5–10 years	63 (23.60%)	25 (22.7%)	38 (24.1%)	
≥ 10years	17 (6.37%)	5 (4.6%)	12 (7.6%)	
HbA_{1C} (%)	7.56 ± 1.55	7.66 ± 1.74	7.49 ± 1.42	0.392
FPG (mmol/L)	7.47 ± 2.47	7.60 ± 2.78	7.40 ± 2.24	0.509
ALT (IU/L)	28.32 ± 30.62	27.36 ± 21.23	29.02 ± 35.91	0.666
Scr (μmol/L)	69.07 ± 24.70	65.11 ± 11.41	71.68 ± 30.50	0.033*
Uric acid (μmol/L)	342.62 ± 88.04	326.00 ± 84.56	353.82 ± 89.35	0.011*
K^+ (mmol/L)	3.91 ± 0.33	3.92 ± 0.30	3.91 ± 0.36	0.825
Na^+ (mmol/L)	145.70 ± 76.81	141.04 ± 2.13	140.97 ± 2.37	0.798
Cl^- (mmol/L)	104.49 ± 2.53	104.80 ± 2.35	104.27 ± 2.64	0.092
Ca^{2+} (mmol/L)	2.34 ± 0.10	2.35 ± 0.10	2.34 ± 0.10	0.830
P^{3+} (mmol/L)	1.18 ± 0.17	1.19 ± 0.17	1.18 ± 0.17	0.474

Note: PA, physical activity; PIA, physical inactivity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 Diabetes Mellitus; HbA_{1C}, glycosylated hemoglobin A_{1c}; FPG, fast plasma glucose; ALT, alanine aminotransferase; Scr, Serum creatinine; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; m-Alb/Cr: the ratio of urinary micro albumin to creatinine; CRP, C-reactive protein; PTH, parathyroid hormone.

	Total (N = 268)	PA group (N = 110)	PIA group (N = 158)	P value
Triglycerides (mmol/L)	2.25 ± 2.07	2.04 ± 1.34	2.40 ± 2.45	0.157
Total Cholesterol (mmol/L)	4.20 ± 1.23	4.07 ± 1.27	4.40 ± 1.14	0.031*
HDL-C (mmol/L)	1.08 ± 0.27	1.12 ± 0.30	1.05 ± 0.26	0.051
LDL-C (mmol/L)	2.41 ± 0.91	2.30 ± 0.91	2.56 ± 0.90	0.021*
m-Alb/Cr	7.75 ± 22.42	3.99 ± 9.08	10.41 ± 26.47	0.015*
CRP (mg/L)	3.66 ± 5.95	4.07 ± 8.67	3.43 ± 3.57	0.591
Free T3 (pg/ml)	3.33 ± 0.45	3.34 ± 0.41	3.31 ± 0.46	0.652
Free T4 (ng/dl)	0.89 ± 0.16	0.90 ± 0.19	0.89 ± 0.13	0.531
Total T3 (ng/ml)	0.88 ± 0.17	0.88 ± 0.17	0.88 ± 0.17	0.971
Total T4 (ug/dl)	7.89 ± 1.45	7.88 ± 1.49	7.92 ± 1.34	0.859
TSHu (IU/ml)	1.93 ± 1.12	1.80 ± 1.07	2.02 ± 1.11	0.102
PTH (pg/ml)	43.20 ± 23.81	41.79 ± 8.58	44.36 ± 20.54	0.218
Thyroid nodule (n, %)	138 (51.5%)	58 (52.7%)	80 (50.6%)	0.804
Smoking (n, %)	85 (31.7%)	37 (33.6%)	48 (30.4%)	0.344
Drinking (n, %)	64 (23.9%)	24 (21.8%)	40 (25.3%)	0.265
Depression/anxiety (n, %)	7 (2.6%)	3 (2.7%)	4 (2.5%)	>0.05
Sleep disorders (n, %)	16 (6.0%)	7 (6.4%)	9 (5.7%)	0.800
Family history of hypertension (n, %)	52 (19.4%)	21 (19.1%)	31 (19.6%)	>0.05

Note: PA, physical activity; PIA, physical inactivity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 Diabetes Mellitus; HbA_{1C}, glycosylated hemoglobin A_{1c}; FPG, fast plasma glucose; ALT, alanine aminotransferase; Scr, Serum creatinine; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; m-Alb/Cr: the ratio of urinary micro albumin to creatinine; CRP, C-reactive protein; PTH, parathyroid hormone.

Newly-onset hypertension and related CVDs

As is showed in Table 2, during 5 years of follow-up, we recorded a total of 145 coronal AS, which included 46 (42.7%) in the PA group and 98 (62%) in the PIA group, the risk of coronal AS was obviously lower in the PA group, compared to the PIA group ($p<0.01$). The total prevalence of CHD in this retrospective cohort was 39.9%. Compared to those in the PIA group, patients in the PA group had a

significantly lower incidence of CHD (30% *vs* 46.8%, p<0.01). In addition, we observed that the incidence of hypertension had significantly difference in the two groups, patients in the PA group had significantly lower incidence than those in the PIA group (15.5% *vs* 35.4%, p<0.01). We also observed that the incidence of carotid/femoral AS was lower in the PA group than in the PIA group, though it had no significance (49.5% *vs* 61.1%, p = 0.051). However, there was no significant difference in terms of the incidence of cerebral ischemic focus, percutaneous coronary intervention (PCI), and myocardial bridge.

Table 2
Newly onset hypertension and related CVDs during follow-up period

	Total (N = 268)	PA group (N = 110)	PIA group (N = 158)	P value
Femoral/carotid AS (n, %)	150 (56.2%)	54 (49.5%)	96 (61.1%)	0.051
Coronary AS (n, %)	145 (54.1%)	46 (42.7%)	98 (62%)	0.002**
Cerebral ischemic focus (n, %)	66 (24.6%)	24 (21.8%)	42 (26.6%)	0.591
CHD (n, %)	107 (39.9%)	33 (30%)	74 (46.8%)	0.006**
Hypertension (n, %)	73 (27.2%)	17 (15.5%)	56 (35.4%)	0.000**
PCI (n, %)	61 (22.8%)	19 (18.2%)	41 (25.9%)	0.142
Coronary artery bypass graft (n, %)	18 (6.7%)	6 (5.5%)	12 (7.6%)	0.622

Note: PA, physical activity; PIA, physical inactivity; CVDs, cardiovascular diseases; AS, atherosclerosis; CHD, coronary heart disease; PCI, percutaneous coronary intervention.

Univariate and multivariate logistic regressions for new-onset hypertension in pre-hypertension patients with T2DM

Unadjusted and adjusted ORs for new-onset hypertension of the whole cohort are shown in Table 3. The univariate and multivariate analysis showed that BMI (univariate: OR 1.126, 95% CI: 0.504 to 1.842, P<0.05; multivariate: OR 1.138, 95% CI: 1.019 to 1.272, p<0.05), HbA_{1C} (univariate: OR = 1.129, 95% CI: 1.016–1.253,P<0.05; multivariate: OR 1.206, 95% CI: 1.006 to 1.446, p<0.05), and physical exercise (univariate: OR 0.333, 95% CI: 0.181 to 0.613, P<0.01; multivariate: OR 0.337, 95% CI: 0.168 to 0.677, p<0.01), were independently associated with new-onset hypertension in T2DM patients.

Table 3
Univariate and multivariate ORs for new-onset hypertension in pre-hypertension T2DM participants

Variables	Univariate		Multivariate	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
Age	1.029 (0.998–1.060)	0.067	1.032 (0.990–1.076)	0.136
Gender (Female)	0.963 (0.504–1.842)	0.910	1.739 (0.729–4.146)	0.212
BMI	1.126 (1.023–1.240)	0.015 *	1.138 (1.019–1.272)	0.022 *
FPG	1.121 (0.945–1.331)	0.190	0.971 (0.724–1.302)	0.845
Scr	1.008 (0.997–1.018)	0.159	1.012 (0.999–1.024)	0.070
Triglycerides	1.033 (0.913–1.169)	0.604	0.940 (0.806–1.097)	0.434
Total cholesterol	1.108 (0.891–1.378)	0.358	1.242 (0.939–1.643)	0.128
HbA_{1C}	1.129 (1.016–1.253)	0.024 *	1.206 (1.006–1.446)	0.043 *
Years of diabetes	1.052 (0.972–1.138)	0.206	1.051 (0.952–1.159)	0.325
Drinking	1.571 (0.858–2.879)	0.143	1.551 (0.731–3.291)	0.253
Smoking	1.172 (0.662–2.074)	0.586	1.171 (0.569–2.407)	0.668
Regular physical activity	0.333 (0.181–0.613)	<0.001**	0.337 (0.168–0.677)	0.002**

Note: T2DM, type 2 Diabetes Mellitus; BMI, body mass index; FPG, fast plasma glucose; Scr, Serum creatinine;HbA_{1C}, glycosylated hemoglobin A_{1c}.

Univariate and multivariate logistic regressions for new-onset hypertension in the subgroup analysis by BMI

To further identify the impact of baseline overweight on the risk of new-onset hypertension in pre-hypertension patients with T2DM, univariate and multivariate logistic regressions analysis was performed (Table 4). We defined overweight as BMI ≥ 25 kg/m^2 and used this to subdivide the T2DM patients into an overweight group (n = 142) and a non-overweight group (n = 126). In the overweight group, univariate logistic regression analysis found that the risk of new-onset hypertension was significantly associated with age (OR 1.041; 95% CI 1.001 to 1.083; $p<0.05$) and regular physical exercise (OR 0.219; 95% CI 0.085 to 0.567; $p<0.01$). And we found that regular physical exercise (OR 0.187; 95% CI 0.063 to 0.558; $p<0.01$) remained as the protective factor for new-onset hypertension in the multivariate logistic regressions analysis. In the non- overweight group, there was no significantly association between regular physical exercise and new-onset hypertension in T2DM patients.

Table 4
Univariate and multivariate ORs for new-onset hypertension in the Subgroup by BMI

Variables	Univariate		Multivariate	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
BMI<25 (N = 126)				
Age	1.021 (0.972–1.073)	0.403	1.026 (0.956-1.100)	0.482
Gender (Female)	1.268 (0.509–3.156)	0.610	4.043 (0.923–17.716)	0. 064
FPG	1.092 (0.938–1.270)	0.256	1.173 (0.867–1.586)	0.302
Scr	1.004 (0.992–1.016)	0.490	1.014 (1.000-1.029)	0.046 *
Triglycerides	1.104 (0.927–1.315)	0.267	0.992 (0.774–1.270)	0.947
Total cholesterol	1.457 (1.054–2.015)	0.023 *	1.611 (1.012–2.565)	0.045 *
HbA_{1C}	1.014 (0.778–1.320)	0.920	0.764 (0.468–1.249)	0.283
Years of diabetes	0.199 (0.967–1.249)	0.150	1.100 (0.940–1.289)	0.235
Drinking	3.036 (1.140–8.086)	0.026 *	2.695 (0.702–10.347)	0.149
Smoking	2.035 (0.834–4.963)	0.118	4.149 (1.106–15.561)	0.035 *
Regular physical activity	0.573 (0.242–1.359)	0.206	0.627 (0.217–1.812)	0.389
BMI ≥ 25 (N = 142)				
Age	1.041 (1.001–1.083)	0.044 *	1.039 (0.984–1.096)	0.170
Gender (Female)	0.897 (0.341–2.361)	0.826	1.980 (0.514–7.625)	0.231
FPG	1.158 (0.995–1.348)	0.059	1.298 (0.997–1.691)	0.053
Scr	1.016 (0.996–1.037)	0.113	1.023 (0.996–1.051)	0.101
Triglycerides	0.954 (0.789–1.154)	0.629	0.924 (0.739–1.155)	0.487
Total cholesterol	0.864 (0.632–1.178)	0.356	1.051 (0.713–1.549)	0.802
HbA_{1C}	1.207 (0.958–1.521)	0.110	1.076 (0.722–1.605)	0.718
Years of diabetes	1.028 (0.930–1.135)	0.594	0.987 (0.865–1.126)	0.847
Drinking	0.957 (0.439–2.083)	0.911	1.374 (0.511–3.692)	0.529
Smoking	0.763 (0.359–1.619)	0.480	0.726 (0.274–1.926)	0.520

Note: BMI, body mass index; FPG, fast plasma glucose; Scr, Serum creatinine;HbA_{1C}, glycosylated hemoglobin A_{1c}.

Variables	Univariate		Multivariate	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
Regular physical activity	0.219 (0.085–0.567)	0.002**	0.187 (0.063–0.558)	0.003**

Note: BMI, body mass index; FPG, fast plasma glucose; Scr, Serum creatinine;HbA_{1C}, glycosylated hemoglobin A_{1c}.

Univariate and multivariate logistic regressions for new-onset hypertension in the subgroup analysis by HbA_{1C}

HbA1C level is utilized clinically as an indicator of the adequacy of glycemic control over several months prior to testing. To explore the impact of baseline HbA_{1C} on the risk of new-onset hypertension in the T2DM patients, we performed subgroup analysis according to HbA_{1C} level. The American Diabetes Association has recommended that an HbA_{1C} breakpoint of 7% would realize the greatest cardiovascular benefit [23]. As is showed in Table 5, our results revealed that in the glucose well controlled group (HbA_{1C}<7%), regular physical exercise (OR = 0.309, 95% CI: 0.114–0.834, p<0.05) was associated with the incidence of new-onset hypertension in T2DM patients. After adjusting for confounding factors, regular physical exercise (OR = 0.385, 95% CI: 0.118–1.261, p = 0.115) was no longer the related factor. In the glucose poorly controlled group (HbA_{1C}≥7%), both univariate and multivariate analysis suggested that regular physical exercise (univariate: OR 0.349; 95% CI 0.160 to 0.760; p<0.01; multivariate: OR 0.349; 95% CI 0.138 to 0.880; p<0.05) was the independent associated factor of the incidence of new-onset hypertension in T2DM patients.

Table 5
Univariate and multivariate ORs for new-onset hypertension in the subgroup by HbA_{1C} level

Variables	Univariate		Multivariate	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
HbA_{1C} level<7 (N = 111)				
Age	1.070 (1.019–1.124)	0.007 **	1.087 (1.008–1.172)	0.029 *
Gender (Female)	0.936 (0.349–2.512)	0.896	0.959 (0.241–3.818)	0.953
BMI	1.036 (0.890–1.206)	0.646	1.112 (0.907–1.362)	0.308
Glucose	0.999 (0.703–1.418)	0.994	0.941 (0.603–1.469)	0.789
Scr	1.006 (0.994–1.019)	0.302	1.006 (0.993–1.020)	0.354
Triglyceride	1.049 (0.766–1.436)	0.765	1.023 (0.684–1.530)	0.911
Cholesterol	1.178 (0.805–1.724)	0.398	1.816 (1.048–3.148)	0.034 *
Years of diabetes	1.163 (1.036–1.304)	0.010 *	1.094 (0.951–1.260)	0.210
Drinking	1.227 (0.486–3.098)	0.665	1.081 (0.319–3.659)	0.901
Smoking	1.255 (0.511–3.084)	0.620	1.422 (0.423–4.779)	0.569
Regular physical activity	0.309 (0.114–0.834)	0.020 *	0.385 (0.118–1.261)	0.115
HbA_{1C} level≥7 (N = 157)				
Age	1.000 (0.962–1.040)	>0.05	1.016(0.963–1.072)	0.566
Gender (Female)	0.982 (0.415–2.320)	0.967	2.656 (0.793-8.900)	0.113
BMI	1.1195 (1.053–1.357)	0.006 **	1.193 (1.033–1.033)	0.017 *
Glucose	1.218 (1.064–1.393)	0.004 **	1.304 (1.096–1.550)	0.003 **
Scr	1.010 (0.991–1.030)	0.296	1.024 (0.998–1.051)	0.067
Triglyceride	1.035 (0.902–1.186)	0.625	0.946 (0.793–1.129)	0.540
Cholesterol	1.080 (0.825–1.414)	0.575	1.096 (0.763–1.574)	0.620
Years of diabetes	0.942 (0.832–1.067)	0.350	0.949 (0.819–1.101)	0.492
Drinking	1.895 (0.849–4.228)	0.118	2.503 (0.887–7.070)	0.083
Smoking	1.126 (0.536–2.362)	0.754	0.815 (0.303–2.188)	0.684

Note: BMI, body mass index; FPG, fast plasma glucose; Scr, Serum creatinine;HbA_{1C}, glycosylated hemoglobin A_{1c}.

Variables	Univariate		Multivariate	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
Regular physical activity	0.349 (0.160–0.760)	0.008 **	0.349 (0.138–0.880)	0.026 *

Note: BMI, body mass index; FPG, fast plasma glucose; Scr, Serum creatinine;HbA_{1C}, glycosylated hemoglobin A_{1c}.

Discussion

T2DM and hypertension often coexist, and there is a considerable overlap between their complications and mechanisms. Most patients with T2DM display dyslipidemia, hypertension and hyperinsulinemia, which are associated with metabolic syndrome and will lead to an increased risk of premature CVDs [24]. Comorbid conditions and complications are considered to determine the quality of life of patients with T2DM [25]. Standards of medical care in diabetes recommended that patients living with diabetes were engaged in regular aerobic activity, resistance or flexibility exercises to realize benefits on metabolism, fitness, and wellbeing. Many studies have elucidated the effects of different exercises on glycemic control, and cardiovascular risk factors in patients with T2DM. However, no cohort study assessed the influence of long-term regular physical activity on new-onset hypertension in T2DM population with pre-hypertension. To the best of our knowledge, this is the first study to investigate the relationship between long-term regular physical exercise and new-onset hypertension in pre-hypertension patients with T2DM.

So far, research concerning the relationship between physical activity and diabetic CVDs were numerous. A meta-analysis study conducted by Bei Pan including total of 37 studies with 2208 patients with T2DM was summarized that aerobic, resistance exercise, and combined exercise have pronounced improvement in HbA1c levels and reduction of CVDs risk factors, including TC, TG, LDL and HDL [26]. Another meta-analysis showed that exercise training, in particular aerobic and combined exercise, improved endothelial function, the indicator of CVDs, in T2DM patients [27]. In these studies the meta-analysis included, the duration of exercise was not long, ranged of 8 weeks to 6 months. That's not long enough to evaluate the long-term influence of physical activity on diabetic complications. More recently, this point also confirmed by a randomized controlled trials, which reporting that combined (resistance-aerobic) exercise training for eight weeks showed a negative result on the serum kinesin-1 level in T2DM patients with diabetic peripheral neuropathy [28]. Hypertension is a major risk factor for CAD, stroke, kidney disease, and mortality. However, the evaluate indicators in these studies were CVDs related factors, such as TC, TG, HDL and endothelial function, et al. Compared with the indicators of new cases of hypertension, these indicators are not intuitive. This study included 268 subjects with a 5-year follow-up provided evidence that there was a significant association between long-term regular physical activity and the incidence of new-onset hypertension among pre-hypertension patients with T2DM. We also found that pre-hypertension T2DM patients with a long-term regular physical activity lifestyle were less likely to have hypertension when compared to the inactivity population (15.5% vs 35.4%, $p<0.01$). Of note, physical exercise (OR 0.337, 95% CI: 0.168 to 0.677, $p<0.01$), BMI (OR 1.138, 95% CI: 1.019 to 1.272, $p<0.05$) and

HbA_{1C} (OR 1.206, 95% CI: 1.006 to 1.446, p<0.05) were the main associated factors for incidence of new-onset hypertension in pre-hypertension patients with T2DM. In this study, long-term regular physical activity might be advantageous in the prevention of new-onset hypertension among T2DM patients with pre-hypertension.

T2DM is a disease that needs long-term lifestyle management. Estimate 80% of people with T2DM are overweight or obese, and many have mobility problems. It has been reported that overweight and obesity are highly prevalent in T2DM patients with high CVD risk and that BMI and waist circumference are related to major cardio metabolic risk factors such as hypertension and elevated LDL-C [29]. In this study, BMI and HbA_{1C} were the independent risk factor for new-onset hypertension in T2DM patients. Further, the confounding effects of BMI and HbA_{1C} on the incidence of new-onset hypertension in T2DM patients with pre-hypertension were analysis in the subgroup. Subgroup analysis indicated that for the overweight T2DM patients, regular physical activity (univariate: OR 0.219; 95% CI 0.085 to 0.567; p<0.01; multivariate: OR 0.187; 95% CI 0.063 to 0.558; p<0.01) was the independent protective factor for the incidence of new-onset hypertension. But it was not in the non-overweight group.

$HgbA_{1c}$ level is utilized clinically as an indicator of the adequacy of glycemic control over several months prior to testing. Thus, it is felt to reflect the effectiveness of long-term glucose control in diabetes patients. Several studies have shown that $HgbA_{1c}$ is associated with the severity and progression of coronary atherosclerosis [30, 31]. One clinical study conducted by R. Huang et al. aiming to scrutinize the relationship between HbA_{1c} and myocardial perfusion in patients with T2DM showed that optimal glycemic control is associated with a preservation of myocardial blood flow reserve (MBFR) in T2DM patients who are at risk for CAD[32]. In this study, HbA1C was the independent risk factor for new-onset hypertension in T2DM patients. Furthermore, subgroup analysis suggested that in the glucose poorly controlled population, regular physical activity (univariate: OR 0.349; 95% CI 0.160 to 0.760; p<0.01; multivariate: OR 0.349; 95% CI 0.138 to 0.880; p<0.05) was significantly related to the lower incidence of new-onset hypertension compared with the T2DM patients with inactivity lifestyle. These results suggested that regular physical activity was the main protective factor for new-onset hypertension in overweight and glucose poorly controlled T2DM patients with pre-hypertension, rather than whose well controlled.

Study Limitation

This study has some limitations. First, this is a retrospective cohort study, the findings should be confirmed by future prospective cohort studies. Second, in this retrospective study, we defined hypertension as taking antihypertensive medications and/or having SBP/DBP ≥ 140/90 mm Hg based on a one-time BP measurement, although current clinical guidelines recommend the mean value of two measurements on at least two different occasions. Third, the follow-up period was only 5 years, and the data regarding changes in lifestyle during follow-up period was absence. However, our study was consisted only long-term regular physical activity population, suggesting that the impact of lifestyle

changes during follow-up period was minimal in our study. Fourth, we cannot obtain other important variables from the electronic database, such as the history of hypertension, change trajectory of blood pressure, fat distribution and weight changes (waist circumference and waist–hip ratio). It is worth mentioning that this study has several highlights. All subjects in this study were T2DM patients with pre-hypertension, which is the high risk stage of developing hypertension.

Conclusion

In conclusion, in this study, long-term regular physical activity may be an important protective factor for new-onset hypertension in pre-hypertension patients with overweight, poor blood glucose control and T2DM at baseline. Our findings suggested that diabetes pre-hypertensive patients should be advised to take physical activity and long-term implementation in order to achieve great cardiovascular benefits.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Zhejiang Hospital. The data are anonymous, and the requirement for informed consent was therefore waived by the ethics committee of Zhejiang Hospital. All research procedures in this study involving human participates were performed according to the ethical standards of the Zhejiang hospital and/or national research committee and the criteria of the declaration of Helsinki (1964) and its later amendment or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the ethics committee of Zhejiang Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The need of informed consent was waived by the ethics committee of Zhejiang Hospital. Correspondence and requests for data should be addressed to Q.Wu and with permission of the ethics committee of Zhejiang Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The conception and design of the study (Q. Wu, J.M. Zhou), acquisition and analyze of data (X.L. Lv, R.F. Zhou), draft, revised article and finished the submission (Q. Wu), collected literature and polished the language for revised manuscript (B.Z. Wang). The other co-authors do not have any conflict of interest. All authors read and approved the final manuscript

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Figures

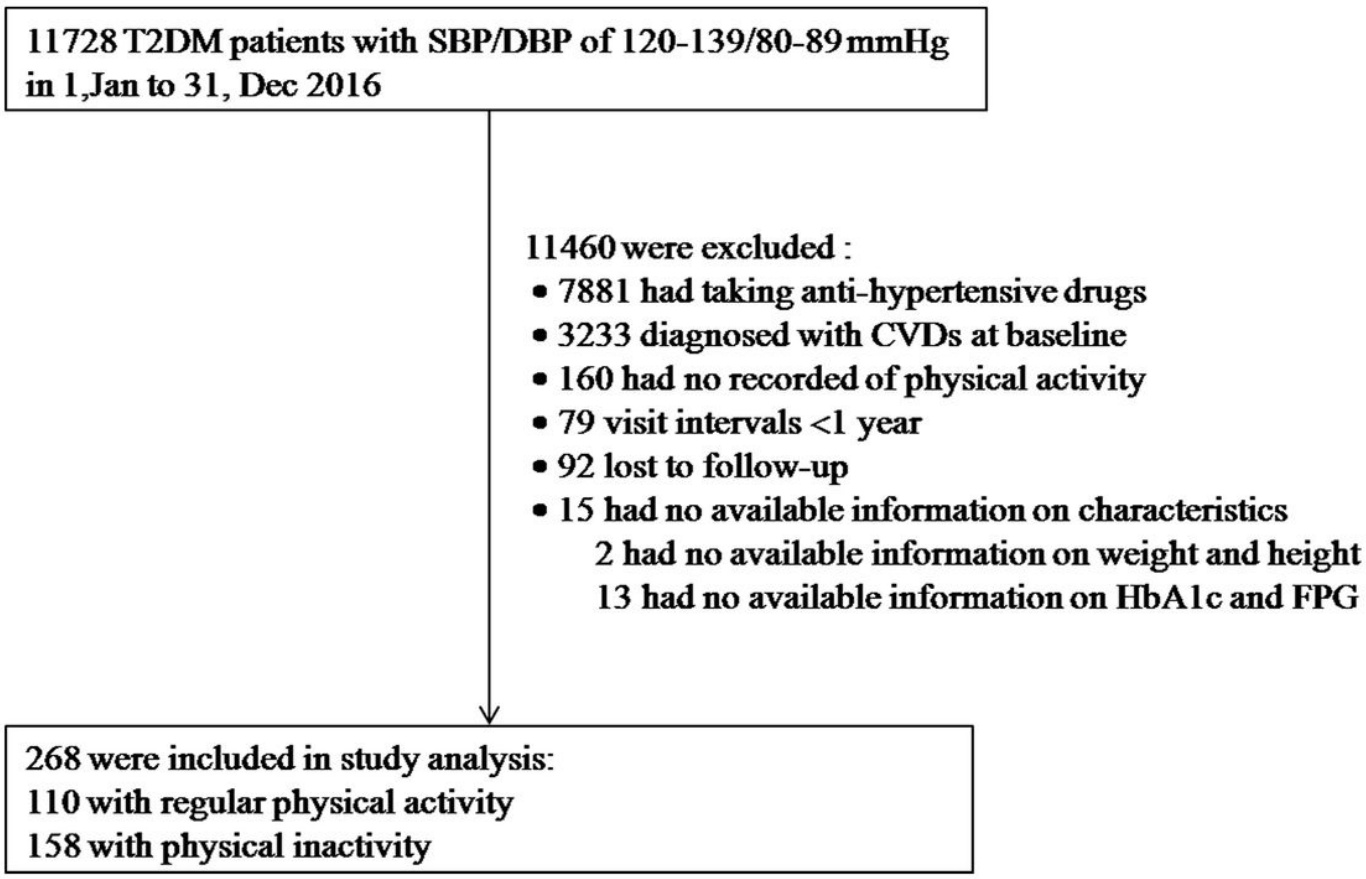

Figure 1

Flow chart of study participants