The Effect of Physical Activity on Diabetic Nephropathy

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Abstract: Exercise plays an important part in diabetes prevention and treatment. Previous meta-analyses revealed that exercise can reduce hemoglobin A1C levels by approximately 0.6% in patients with type 2 diabetes mellitus. The beneficial effects of exercise include improved cardiovascular fitness, reduced blood pressure, and improved lipid profiles. Oxidative stress and inflammatory markers are also reduced after exercise. As glycemic control, blood pressure control, and oxidative stress are believed to play an integral role in the pathogenesis of diabetic nephropathy, it is logical to hypothesize that exercise has beneficial effects against diabetic nephropathy. However, few studies have focused on this topic, and their results were inconclusive. **Purpose:** The study was designed to observe the effect of physical activity on nephropathy in patients with type 2 diabetes mellitus. **Method:** In total, 1232 patients with type 2 diabetes mellitus (age 18–75 years) who were followed up regularly for more than 1 year from 2008 to 2010 at Chia-Yi Christian Hospital were enrolled. These patients completed a physical activity questionnaire and a basic characteristics evaluation annually and biochemistry tests periodically (3–12 months). They are divided to sedentary group, low physical activity group and adequate physical activity group according to their metabolic equivalent. **Results:** The adequate physical activity group was older (58.93±10.08 years vs. 55.21±10.34 years), and patients in this group had a longer duration of diabetes and lower frequencies of smoking and betel nut chewing habits. Males were more likely to engage in physical activity. Waist circumference, body weight, blood glucose and triglyceride, microalbuminuria, and the estimated glomerular filtration rate (eGFR) were significantly lower in the adequate physical activity group. After follow-up for more than 1 year, urinary albumin levels were decreased in the physical activity group, albeit without statistical significance. Paradoxically, eGFR was improved significantly in the low physical activity group. In a generalized estimation equation logistic regression model, physical activity displayed borderline significance in reducing urine protein levels by >50% in the macroalbuminuria group (odds ratio [OR]=2.87, P=0.093), whereas it was not a significant factor in the entire patient population (OR=1.13, P=0.593).

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1. Introduction

Exercise plays an important part in diabetes prevention and management (Tuomilehto et al., 2001; Wing, 2010). Previous studies found that exercise can reduce hemoglobulin A1C levels in patients with type 2 diabetes mellitus (Boule, Haddad, Kenny, Wells, Sigal, 2001) as well as improve cardiovascular fitness, reduce blood pressure and improve lipid profile (Boule, Haddad, Kenny, Wells, Sigal, 2001; Chudyk & Petrella, 2011; Thomas, Elliott, & Naughton, 2006). Oxidative stress and inflammation were also improved after exercise (Choi et al., 2012; Golbidi, Badran, & Laher, 2012). Diabetic nephropathy is a severe chronic complication (Gross, de Azevedo, Silveiro, Canani, Caramori, & Zelmanovitz, 2005) that can lead to renal failure and adverse cardiovascular outcomes (Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2005). The pathogenesis of diabetic nephropathy is attributable to hyperglycemia and increased oxidative stress, cytokine levels and inflammation, which might result in proteinuria and glomerulosclerosis (Yamagishi & Matsui, 2010). The management of nephropathy including glycemic control and blood pressure control and use of angiotension converting enzyme inhibitor (ACEI) or angiotension receptor blocker (ARB)(U.K. Prospective Diabetes Study Group, 1995; Heerspink et al., 2010; Brenner et al., 2001). The role of exercise in diabetic nephropathy is not well known. In animal studies, exercise reduced advanced glycosylation end products (AGEs) and oxidative stress and reduced proteinuria and preserved renal podocyte (Boor et al., 2009; Ishikawa et al., 2012). In humans, a small study revealed that after 6 months of aerobic exercise, proteinuria was improved, but the improvement was unrelated to improvements in insulin resistance and oxidative stress (Lazarevic et al., 2007). In another study of patients with type 2 DM in chronic kidney disease stage 2-4, 24 weeks of exercise did not significantly affect the estimated glomerular filtration rate (eGFR), proteinuria, or high-sensitivity C-reactive protein (hs-CRP) and hemoglobulin A1C levels (Leehey et al., 2009). In patients with end-stage renal disease, progressive exercise improved erythropoietin synthesis, patient quality of life, and exercise performance (Painter, Carlson, Carey, Paul, & Myll, 2000a, 2000b). Therefore, in this study, we assessed whether exercise is an important factor for diabetic nephropathy and whether the effects of exercise on albuminuria varied by stage of albuminuria.

2. Research Design and Methods

2.1 Participants

Patients with type 2 diabetes who regularlyvisited the endocrinology and metabolism outpatient department of Chia-Yi Christian Hospital were enrolled. These type 2 diabetic patients were 18-75 y/o and received self-management education program regularly from January 2008 to December 2011. Patients' data were collected untill January 2013. Those who were type 1 diabetes mellitus and those with incomplete data were excluded.

2.2 Physical activity evaluation

Physical activity (PA) was assessed by international physical activity questionaaire short form that has been validated to assess PA in Taiwan. Participants were asked to report physical activity for lasting at least 10 minutes per session in the past 7 days. The American College of Sports Medicine and American Diabetes Association suggests that individuals obtain 75 minutes of vigorous aerobic exercise per week, or 150 minutes of moderate aerobic exercise per week, or an equivalent combination or those who had mixed exercise including light, moderate or vigorous physical activity reaching 600 MET-min/week were defined as adequate physical activity. Those who did not have physical activity were defined as sedentary group. Those who had physical activity but did not reach 600 MET-min/week threshold comprised the inadequate physical activity group.

2.3 Baseline assessments and yearly follow-up

A detailed medical evaluation was performed at baseline and each year thereafter. The evaluation included a demographic and anthropometric examination, and a drugs history evaluation. Systolic (SBP) and diastolic blood pressure (DBP) were measured from the arm in seated position after a 5 min rest. Waist circumference is measured at a level midway between the lowest rib and the iliac crest. BMI was calculated as weight (kg) / height (m^2).

2.4 Biochemical analyses

Urine and blood samples were obtained for biochemical analyses after an overnight fast of 12 hours every 3-12 months. Hemoglobulin A1C, urinary albumin excretion, fasting glucose, and ceatinine levels as well as lipid and liver profile were assessed using a Tosoh G8 HPLC analyzer and a Hitachi 7170 chemistry analyzer respectively. Estimated glomerular filtration rate (eGFR) was calculated with modified diet in renal disease (MDRD) equation. A total of 1232 patients fulfilled the inclusion criteria. Of these, 627 patients were included in the sedentary group, 312 patients were included in the inadequate physical activity group, and 293 patients were included in the adequate physical activity group.

2.5 Statistical analyses

Continuous variables were expressed as mean and standard deviation (SD). Chi square was used for categorical variables. ANOVA was used for analyses of baseline data. These patients had followed up at least 1 year and 80% had followed up for 2 years. The differences of anthropometric and biochemistry data were collected. Generalized estimation equation (GEE) was used for regression analyses. Every patient had multiple measurements of hemoglobin A1c, lipid profile and microalbuminuria etc. was grouped as a cluster and logistical regression analysis to predict odd ratio of each factor for microalbuminuria reduction more than 50%. Besides we divided patients according to their proteinuria stage for subgroup analyses. SPSS 21.0 (Statistical package for the social science 21.0 version) was used for analyses.

3. Result

The Baseline characteristics of the study patients are summarized in table 1. Subjects in sedentary group were younger and they had shorter duration of diabetes mellitus and higher frequencies of current smoking and betel nut chewing. Fasting plasma glucose, and hemoglobin A1C, triglyceride and diastolic blood pressure were better in adequate PA group. Although microalbumunuria was more severe in the sedentary group, the eGFR values of this group were better.

At baseline, there were no differences in the use of oral antidiabetic agent, insulin, ACEIs or ARBs, statin or antiplatelet drugs. However, insulin therapy was significantly less common in adequate PA group after 1 year of follow-up. (Table 2)

Table 1. Basic characteristics of study subjects

	Sedentary (n=627)	Inadequate PA (n=312)	Adequate PA (n=293)	*P* value
Age (y/o)	55.2±10.3	58.1± 10.3[a]	58.9±10.1[c]	<0.001
DM duration (y)	5.1 ± 5.6	6.1 ± 6.2[b]	6.6 ± 7.0[d]	0.003
Sex (M/F) (%)	53.4/46.6	41.7/58.3	51.9/48.1	0.002
Smoker (%)	23.3	10.9[b]	16.4[e]	<0.001
Betel nut chewing (%)	8	5.1	2.1	0.006
BW (Kg)	68.87± 13.74	66.51 ± 11.53[b]	67.17 ± 12.24	0.017
Waist (cm)	91.62 ± 10.61	90.03 ± 9.28	89.76 ± 10.23d	0.016
BMI (kg/m2)	25.38 ± 26.23	24.21 ± 8.31	24.42 ± 6.93	0.625
Exercise volume (MET/hr/wk)	0	5.98 ± 2.61	22.03 ± 12.9	<0.001
Fasting glucose (mg/dl)	150.68 ± 51.71	142.81 ± 46.54	141.54 ± 41.62[d]	0.008
A1C (%)	8.42 ± 2.01	7.91 ± 1.63[a]	7.99 ± 1.69[d]	<0.001
GPT (mg/dl)	41.52 ± 38.13	41.96 ± 45.82	36.04 ± 29.42	0.091
Creatinine (mg/dl)	0.97 ± 0.34	0.99 ± 0.35	1.00 ± 0.32	0.366
Total choesterol (mg/dl)	191.54 ± 41.61	186.59± 35.70	185.16 ± 36.80	0.037
triglyceride (mg/dl)	165.54 ± 155.52	140.21 ± 80.38[b]	131.86 ± 73.82[c]	<0.001
HDL-C (mg/dl)	52.93 ± 14.12	52.72 ± 13.53	54.11 ± 14.07	0.402
LDL-C (mg/dl)	113.47 ± 35.21	111.16 ± 31.20	109.52 ± 31.90	0.222
UACR (mg/g)	229.27 ± 1141.53	107.26 ± 558.54	85.21 ± 262.73	0.032
eGFR (ml/min)	82.04 ± 21.95	76.55 ± 21.49[a]	77.56 ± 20.91[d]	<0.001
sBP (mmHg)	139.05 ± 19.52	139.51 ± 19.91	139.11 ± 20.12	0.942
dBP (mmHg)	83.75 ± 11.80	82.67 ± 10.78	81.49 ± 11.13[d]	0.018

[a]sedentary vs inadequate PA $p<.001$, [b]sedentary vs inadequate PA $p<.05$，[c]sedentary vs adequate PA $p<.001$，[d]sedentary vs adequate PA $p<.05$，[e]inadequate PA vs adequate PA $p<.05$

Table 2. drugs history baseline and 1 year after f-u.

Baseline/f-u 1year	Sedentary (n=627)	Inadequate PA (n=312)	Adequate PA (n=293)
OAD	96.7% / 96.7%	97% / 97%	97.6% / 97.6%
Insulin	17.5% / 16.4%[a, b]	16.5% / 11%	19.9% /11.7%
ACEI/ARB	30.9% / 36.5%	34.0% / 34.5%	35.7% / 36.9%
Statin	37.1% / 35.5%	41% / 40.5%	34% / 39.5%
Antiplatelate	8.5% / 18.5%	8.5% / 21%	10.7% / 21%

OAD: oral antidiabetic drug, ACEI: angiotension converting enzyme inhibitor, ARB" angiotensionogen receptor blocker, [a]sedentary vs inadequate PA $p<.05$, [b]sedentary vs adequate PA $p<.05$

The change of physical condition and biochemistry among the patients after more than 1 year of follow up was shown in table 3. The physical activity group had a greater reduction in weight, albeit without significant. No differences in microalbuminuria and eGFR were observes among the three groups.

We performed logistic regression to determin whether physical activity is an important factor for improving proteinuria (>50% reduction). The analysis found that physical activity is not an important factor (figure 1). However years of follow-up (OR 0.45, P< 0.001) and initial hemoglobin A1C (OR 0.87, P=0.034) and the change in BMI (OR 0.84, P=0.005) were identified as significant factors. among patients in microalbuminuria stage, physical activity remained an insignificant factor (Figure 2), but among those in macroalbuminuria stage, physical activity had borderline significant (OR 2.87, P=0.093; Figure 3).

Table 3. biochemistry change after f-u for 1 year 〔mean (95% CI) 〕

	Sedentary (n=627)	Low physical activity (n=312)	Adequate physical activity (n=293)
△ BW (Kg)	ref	-0.12(-0.56-0.33)	-0.22 (-0.66-0.21)
△ waist (cm)	ref	0.02 (-0.45-0.49)	0.03 (-0.45-0.52)
△BMI (kg/m2)	ref	-0.04 (-0.22-0.13)	-0.07 (-0.24-0.10)
△fasting glucose (mg/dl)	ref	5.71(-0.18-11.60)	6.52 (0.60-12.45)
△A1C (%)	ref	0.35 (0.14-0.56)	0.24 (0.01-0.47)
△GPT (mg/dl)	ref	-1.35 (-4.96-2.26)	-0.08 (-3.00-2.84)
△Creatinine(mg/dl)	ref	-0.01 (-0.04-0.02)	-0.02 (-0.04-0.01)
△total cholesterol (mg/dl)	ref	3.21 (-1.25-7.67)	3.37 (-1.11-7.85)
△triglyceride (mg/dl)	ref	7.21 (-7.28-21.70)	12.17 (-1.91-26.25)
△HDL-C (mg/dl)	ref	0.10 (-0.81-1.00)	-0.05 (-1.01-0.91)
△LDL-C (mg/dl)	ref	2.77 (-0.70-6.24)	2.55 (-1.06-6.16)
△UACR (mg/g)	ref	18.13 (-29.66-65.93)	1.09 (-42.90-45.07)
△eGFR (ml/min)	ref	1.62 (0.34-2.89)	0.75(-0.54-2.03)

BMI: body mass index, UACR: urine albumin to creatinine ratio, eGFR: estimated glomerular filtration rate

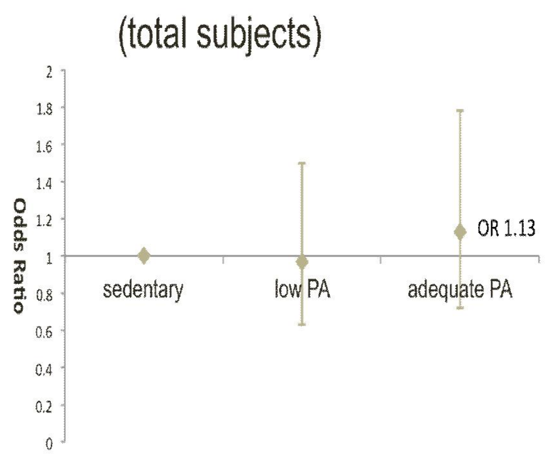

Figure 1: determinant of urine protein > 50% of regression by physical activity group

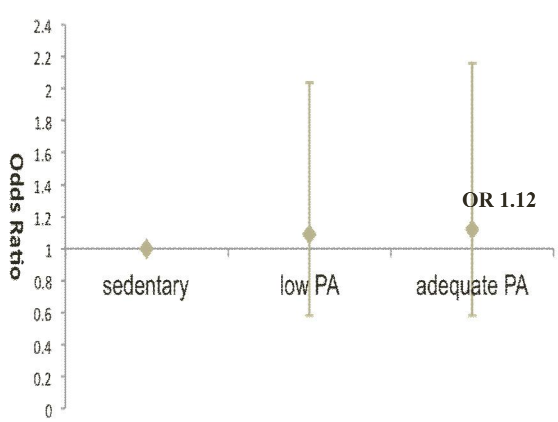

Figure 2. microaluminuria stage : determinant of proteinuria reduction > 50% by physical activity group

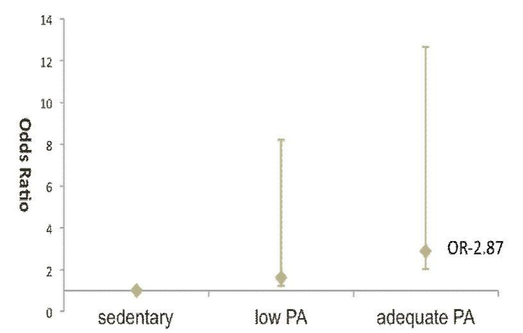

Figure 3. Macroalbuminuria stage: determinant of proteinuria reduction > 50% by physical activity group

4. Conclusion

In this study, patients in the physical activity group were older and a longer duration of diabetes. We also found patients with a duration of t diabetes less than 1 year and longer than 10 years were more likely to engage in physical activity. A previous study noted thtat though lifestyle modifications including diet control and exercise are effective for glycemic control, but this control is difficult to maintain (American Diabetes Association, 2014). When glycemic control worsened, patients often had greater motivation to resume physical activity. In our baseline data, we could observe the relationships between exercise and redyced hemoglobin A1C, triglyeride and microalbuminuria levels. Waist circumference and body weight were lowered significantly by physical activity. In addition, the physical activity group had significantly lower proportions of patients who smoked or chewed betel nut. This finding suggests that physical activity is an indicator of better self-efficacy.

During follow up for more than 1 year, physical activity group did not exhibit better glycemic control. This is in contrast with the findings of previous intervention studies (Boule et al., 2001; Chudyk et al., 2011). This finding may be explained by the lower use of insulin therapy in the physical activity group, which wound negate the benefit of physical activity. Additionally, all three groups received diabetes self-management education, which might also reduce differences among the groups.

In our study we cannot identify physical activity as an important factor for reducing albuminuria, but a trend toward improvement was noted in the macroalbuminuria group. Controversy exists concerning whether physical activity improves nephropathy. A case report in 2004 revealed that glycemic control was improved after 6 weeks of physical activity, whereas microalbuminuria was improved after 24 months (Fredrickson, Ferro, & Schutrumpf, 2004). Another study reported that exercise may improve insulin sensitivity and endothelium function in older men, but the benefit disappeared after 8 weeks of rest (Ratel et al., 2012). These studies intimate that the benefits of physical activity on nephropathy require a longer time and persistent intervention. Moreover, glycemic control and ACEIs or ARBs usage are important components of the management of diabetic nephropathy (11-13). After these standard treatment, the incidence of proteinuria progression reduced to around 3-4% each year (Reutens, 2013). Thus, larger sample sizes and longer observation periods might be needed to observe the benefits.

We use physical activity questionnaire to evaluate patients' physical activity in short period instead of whole year. Although we repeated our questionnaire annually and only included patients in the adequate physical activity who had participated in the physical activity each year. There are still some biases. However one review article showed irrespective of the choice of questionnaire, the correlation of questionnaire with actual physical activity was around 0.71 to 0.96 (Prince et al., 2008).

Although the effect of physical activity on diabetic nephropathy remains controversial, patients with diabetic nephropathy are at high risk of developing cardiovascular disease (Tanaka et al., 2011). Physical activity improves glycemic, blood pressure and lipid control (Boule et al., 2001; Chudyk et al., 2011). These are all important cardiovascular risk factors. Physical activity can also improve patient quality of life too (Painter et al., 2000b; Nicolucci, 2011). Thus, increased physical activity should be encouraged among patients with type 2 diabetes mellitus.

Similarly as observed in a previous study, as diabetes progressed, the prevalence of nephropathy increased (Reutens, 2013). Glycemic control is also an important factor for alleviating proteinuria as reported previously (UK Prospective Diabetes Study Group, 1998; Zoungas et al., 2009). Obesity and overweight are highly correlated with diabetic nephropathy (Maric-Bilkan, 2013; Chen et al., 2013). In our subjects, reductions in body weight had a beneficial effect on proteinuria, as body weight loss might also improve inflammatory response (Choi et al., 2012) and reduced visfatin and increased adiponectin (Kadoglou, Vrabas, Kapelouzou, & Angelopoulou, 2012) , which might promote the alleviation of proteinuria.

5. Conclusion

Adequate physical activity had positive correlation with good glycemic control and lowered triglyceride and microalbuminuria levels. After 1 year, greater reductions in proteinuria were not observed in the adequate physical activity group. In subgroup analysis, a trend toward improvement was observed among patients with macroalbuminuria.

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