

# Physical Activity and Diabetes Complications in Patients With Type 1 Diabetes

## The Finnish Diabetic Nephropathy (FinnDiane) Study

JOHAN WADÉN, MD<sup>1,2</sup>  
 CAROL FORSBLOM, DMSC<sup>1,2</sup>  
 LENA M. THORN, MD<sup>1,2</sup>  
 MARKKU SARAHEIMO, MD<sup>1,2</sup>  
 MILLA ROSENGÅRD-BÄRLUND, MD<sup>1,2</sup>  
 OUTI HEIKKILÄ, MD<sup>1,2</sup>

TIMO A. LAKKA, MD, DMSC<sup>3,4</sup>  
 HEIKKI TIKKANEN, MD, DMSC<sup>1,5</sup>  
 PER-HENRIK GROOP, MD, DMSC<sup>1,2</sup>  
 ON BEHALF OF THE FINNDIANE STUDY  
 GROUP

**P**hysical activity exerts numerous beneficial health effects, and the evidence favoring a physically active lifestyle in the treatment of chronic diseases is substantial (1). For patients with diabetes, physical activity is considered important (2). In theory, regular physical activity may prevent diabetes complications through beneficial effects on glycemic control, insulin sensitivity, blood pressure, lipid profile, and endothelial function. However, physical activity could also cause adverse effects or patients may not be able to exercise due to complications. Little, however, is known about the relationship between physical activity and diabetes complications (3). Therefore, we investigated the associations between physical activity and microvascular and macrovascular diabetic complications in a large cohort of patients with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study.

### RESEARCH DESIGN AND

**METHODS**— The FinnDiane Study and the assessment of self-reported leisure-time physical activity (LTPA) by a

questionnaire have previously been described (4). This is a cross-sectional analysis of 1,945 patients with data on LTPA. Renal status was based on at least three urine collections. Renal function was evaluated by the Cockcroft-Gault formula (5) for estimated creatinine clearance. Data on retinopathy and cardiovascular disease (CVD) were obtained from medical records. Differences between groups were evaluated with the Kruskal-Wallis test for total LTPA; otherwise, the  $\chi^2$  test was used.

**RESULTS**— Mean  $\pm$  SD age was 38.5  $\pm$  12.3 years (range 10.2–81.8), duration of diabetes 23.4  $\pm$  12.8 years (0.3–61.3), BMI 25.1  $\pm$  3.5 kg/m<sup>2</sup>, A1C 8.3  $\pm$  1.4%, and LTPA 19.7 (10.1–35.5) MET h/week; 48.2% of patients were men. Total LTPA was not associated with sex, age, or with duration of diabetes.

Table 1 shows total LTPA, components of LTPA, and previous LTPA habits according to various degrees of diabetes complications. Physical inactivity, as well as low-frequency and low-intensity LTPA, were more common in patients

with diabetic nephropathy and proliferative retinopathy than in those without these complications. Patients with microalbuminuria more frequently reported low-intensity LTPA than those with normal urinary albumin excretion rate ( $P = 0.047$  adjusted for age and sex). Impaired renal function and CVD were also associated with low-intensity LTPA.

We further performed multiple logistic regression models controlling for duration of diabetes, sex, and BMI. Low-frequency LTPA (<1 session/week) (odds ratio 1.90 [95% CI 1.39–2.60]) and low-intensity LTPA (2.31 [1.72–3.10]) were independently associated with diabetic nephropathy, while log-transformed total LTPA was not (0.88 [0.76–1.02]). Low-intensity LTPA, but not total LTPA or low-frequency LTPA, was independently associated with proliferative retinopathy (1.49 [1.15–1.93]) and CVD (2.58 [1.79–3.74]). Additionally controlling for proliferative retinopathy and CVD, low-intensity (1.90 [1.36–2.66]) and low-frequency (1.93 [1.35–2.76]) LTPA were still associated with nephropathy.

**CONCLUSIONS**— Patients with diabetic micro- and macrovascular complications reported different patterns of LTPA compared with patients without complications. The most prominent difference was the intensity of LTPA, since low intensity was clearly associated with impaired renal function and increasing degree of proteinuria, retinopathy, and CVD.

Diabetes complications may limit the patient's ability to exercise by several mechanisms. Patients with proliferative retinopathy are recommended to avoid strenuous activities and Valsalva-like maneuvers because of risk of vitreous hemorrhage (2). CVD is an evident limitation because of possible exercise-induced myocardial ischemia, systolic or diastolic cardiac dysfunction, or ischemia in the lower limbs. Diabetic nephropathy is strongly associated with CVD (6); however, our data support that CVD is not the

From the <sup>1</sup>Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland; the <sup>2</sup>Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland; the <sup>3</sup>Department of Physiology, Institute of Biomedicine, University of Kuopio, Kuopio, Finland; the <sup>4</sup>Kuopio Research Institute of Exercise Medicine, Kuopio, Finland; and the <sup>5</sup>Unit for Sports and Exercise Medicine, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland.

Address correspondence and reprint requests to Per-Henrik Groop, Biomedicum Helsinki, POB 63, 00014 University of Helsinki, Helsinki, Finland. E-mail: per-henrik.groop@helsinki.fi.

Received for publication 29 June 2007 and accepted in revised form 17 October 2007.  
 Published ahead of print at <http://care.diabetesjournals.org> on 24 October 2007. DOI: 10.2337/dc07-1238.

Additional information for this article can be found in an online appendix at <http://dx.doi.org/10.2337/dc07-1238>.

**Abbreviations:** CVD, cardiovascular disease; FinnDiane, Finnish Diabetic Nephropathy; LTPA, leisure-time physical activity.

© 2008 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Physical activity (current and past) in relation to various degrees of diabetes complications

|   | n     | Total LTPA<br>(MET h/week) |                 | Duration<br>≤2 h/week | Duration<br>≤1 session/week in<br>adolescence |                                   | Competitive sports | Decreased last<br>10 years |       |
|---|-------|----------------------------|-----------------|-----------------------|---|-----------------------------------|--------------------|----------------------------|-------|
|   |       | Sedentary                  | <1 session/week |                       | Low intensity                                 | <1 session/week in<br>adolescence |                    |                            |       |
| Normal UAER                                 | 1,108 | 20.3 (10.5–35.0)           | 23.0            | 20.6                  | 21.4  | 22.8                              | 23.3               | 28.6                       | 48.9  |
| Microalbuminuria                            | 223   | 19.9 (9.4–39.7)            | 27.4            | 22.0                  | 30.5*   | 25.5                              | 22.2               | 29.1                       | 50.0  |
| Macroalbuminuria                            | 187   | 18.0 (7.9–31.7)            | 32.1*           | 30.6*                 | 43.7*   | 28.8                              | 16.8               | 33.0                       | 60.4* |
| Dialysis                                    | 21    | 14.5 (2.6–44.3)            | 38.9            | 47.6*                 | 61.9*   | 37.5                              | 25.0               | 9.5                        | 66.7  |
| Renal transplantation<br>(S-Cr >150 μmol/l) | 17    | 8.3 (1.4–24.7)*            | 50.0*           | 37.5                  | 64.7*   | 40.0                              | 25.0               | 23.5                       | 70.6  |
| Renal transplantation<br>(S-Cr ≤150 μmol/l) | 43    | 22.3 (14.7–55.5)           | 18.9            | 23.8                  | 55.8*   | 11.1                              | 16.3               | 32.6                       | 58.1  |
| Renal function                              |       |                            |                 |                       |   |                                   |                    |                            |       |
| Normal                                      | 1,026 | 19.3 (10.5–34.3)           | 23.5            | 21.5                  | 21.5  | 23.8                              | 21.4               | 30.6                       | 50.7  |
| Mildly impaired                             | 521   | 18.9 (9.7–36.4)            | 25.5            | 21.0                  | 29.5†   | 23.5                              | 24.5               | 23.8†                      | 49.1  |
| Impaired                                    | 140   | 23.8 (9.5–35.1)            | 25.9            | 22.6                  | 45.7†   | 21.6                              | 20.1               | 32.1                       | 50.0  |
| Severely impaired                           | 37    | 18.3 (6.3–37.3)            | 30.3            | 43.2†                 | 56.8†   | 28.1                              | 8.3                | 24.3                       | 81.1† |
| Retinopathy                                 |       |                            |                 |                       |   |                                   |                    |                            |       |
| No  | 880   | 19.7 (11.0–35.6)           | 21.7            | 19.2                  | 18.6  | 22.6                              | 22.5               | 31.2                       | 48.3  |
| Background                                  | 399   | 18.9 (9.5–34.3)            | 25.7            | 26.4†                 | 26.5†   | 23.9                              | 19.7               | 28.9                       | 55.4† |
| Proliferative                               | 601   | 19.8 (8.5–35.6)            | 27.9†           | 25.1†                 | 39.3†   | 23.8                              | 21.8               | 27.8                       | 53.3  |
| CVD   |       |                            |                 |                       |   |                                   |                    |                            |       |
| No  | 1,769 | 19.7 (10.2–35.5)           | 24.0            | 22.2                  | 24.1  | 23.4                              | 22.2               | 29.3                       | 50.1  |
| Yes   | 158   | 18.0 (7.7–36.4)            | 28.6            | 23.6                  | 56.4†   | 25.0                              | 17.4               | 31.2                       | 65.6† |
| Diabetic nephropathy                        |       |                            |                 |                       |   |                                   |                    |                            |       |
| Without CVD                                 | 192   | 19.5 (7.5–33.0)            | 32.3            | 31.1                  | 40.5*   | 29.1                              | 18.4               | 30.4                       | 58.5  |
| With CVD                                    | 74    | 17.5 (7.7–39.3)            | 27.6            | 30.1                  | 68.1*§  | 19.2                              | 15.3               | 31.5                       | 67.1  |

Data are medians (interquartile range) or percentages. Sedentary: total LTPA <10 MET h/week. Low-intensity LTPA: very light to light activities, grade 0–1 out of an intensity scale of 0–4. Micro- and macroalbuminuria: urinary albumin excretion rate (UAER) 30–299 and ≥300 mg/24 h (24-h collections) or 20–199 and ≥200 μg/min (overnight collections), respectively, in at least two of three consecutive urine collections. Normal renal function: Cockcroft-Gault-estimated creatinine clearance ≥90 ml/min per 1.73 m<sup>2</sup>; mildly impaired, 60–89 ml/min per 1.73 m<sup>2</sup>; impaired, 30–59 ml/min per 1.73 m<sup>2</sup>; and severely impaired, <30 ml/min per 1.73 m<sup>2</sup>. Cardiovascular disease: symptomatic coronary heart disease, myocardial infarction, coronary artery procedure (bypass surgery or angioplasty), stroke, limb amputation, or peripheral artery procedure. Diabetic nephropathy: macroalbuminuria, dialysis, or renal transplantation. \*P < 0.05 vs. normal urinary albumin excretion rate. †P < 0.05 vs. normal renal function. ‡P < 0.01 vs. none. §P < 0.01 vs. without CVD. S-Cr, serum creatinine.

sole driving force behind reduced LTPA in patients with nephropathy. A decline in renal function, especially when due to diabetic nephropathy (7), is associated with reduced blood hemoglobin concentration as a result of impaired erythropoietin production, which may impair oxygen delivery during exercise. Autonomic neuropathy may cause inadequate responses in heart rate and blood pressure during exercise (8). Peripheral neuropathy and foot ulcers may impair walking and running ability. Diabetes complications, as well as diabetes itself, are further associated with endothelial dysfunction (9,10), which may impair vasodilatation in exercising skeletal muscle tissue. Finally, diabetes complications are associated with depression (11), which may decrease physical activity.

The observed differences in LTPA between patients with various diabetes complications are probably to a large extent due to the abovementioned exercise-limiting factors. However, the difference in LTPA in patients with microalbuminuria compared with a normal urinary albumin excretion rate is a potentially important finding. Microalbuminuria in type 1 diabetes is unlikely to cause exercise intolerance because patients with microalbuminuria usually have normal kidney function. Therefore, it is possible that low LTPA precedes the development of microalbuminuria.

The study includes a large number of patients, and LTPA was assessed by a questionnaire previously validated in a Finnish cohort (12). Objective measurements of LTPA, however, were not performed, and bias due to self-reported LTPA is possible. A limitation is the cross-

sectional study design. A longitudinal study design will be needed to provide evidence for the role of physical activity in the development and progression rate of diabetes complications.

**Acknowledgments**— The study was supported by grants from the Folkhälsan Research Foundation, the Wilhelm and Else Stockmann Foundation, the Sigrid Juselius Foundation, the Waldemar von Frenckell Foundation, the Liv och Hälsa Foundation, the Perklén Foundation, the Finnish Medical Society (Finska Läkaresällskapet), and the European Commission (contract no. QL62-CT-2001-01669).

The skilled assistance of Anna Sandelin, Sinikka Lindh, Susanne Ström, and Jessica Thorn is gratefully acknowledged. Finally, we acknowledge all physicians and nurses at each participating study center, regarding whom information is presented in detail in an online appendix (available at <http://dx.doi.org/10.2337/dc07-1238>).

**References**

1. Pedersen BK, Saltin B: Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports* 16 (Suppl 1):3–63, 2006
2. American Diabetes Association: Physical Activity/Exercise and Diabetes Mellitus (Position Statement). *Diabetes Care* 26 (Suppl. 1):S73–S77, 2003
3. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ: The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study–VII. *J Clin Epidemiol* 44:1207–1214, 1991
4. Wadén J, Tikkanen H, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Lakka T, Riska M, Groop P-H, the FinnDiane Study Group: Leisure time physical activity is

associated with poor glycemic control in type 1 diabetic women: the FinnDiane study. *Diabetes Care* 28:777–782, 2005

5. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
6. Tuomilehto J, Borch-Johnsen K, Molarius A, Forsen T, Rastenyte D, Sarti C, Reunanen A: Incidence of cardiovascular disease in type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia* 41:784–790, 1998
7. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 162:1401–1408, 2002
8. Kahn JK, Zola B, Juni JE, Vinik AI: Decreased exercise heart rate and blood pressure response in diabetic subjects with cardiac autonomic neuropathy. *Diabetes Care* 9:389–394, 1986
9. De Vriese AS, Verbeuren TJ, Van de Voorde J, Lameire NH, Vanhoute PM: Endothelial dysfunction in diabetes. *Br J Pharmacol* 130:963–974, 2000
10. Calver A, Collier J, Vallance P: Inhibition and stimulation of nitric oxide synthesis in the human forearm arterial bed of patients with insulin-dependent diabetes. *J Clin Invest* 90:2548–2554, 1992
11. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ: Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 63:619–630, 2001
12. Lakka TA, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT: Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* 330:1549–1554, 1994