Leisure Time Physical Activity Is Associated With Poor Glycemic Control in Type 1 Diabetic Women

The FinnDiane study

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OBJECTIVE — We studied the association between leisure time physical activity (LTPA) and glycemic control, insulin dose, and estimated glucose disposal rate (eGDR) in type 1 diabetes.

RESEARCH DESIGN AND METHODS — This is a cross-sectional study of 1,030 type 1 diabetic patients participating in the Finnish Diabetic Nephropathy Study, a nationwide multicenter study. LTPA was assessed by a validated 12-month questionnaire and expressed in metabolic equivalent (MET) units. Patients were grouped as sedentary (LTPA <10 MET h/week, $n = 247$), moderately active (LTPA 10–40 MET h/week, $n = 568$), and active (LTPA >40 MET h/week, $n = 215$). Outcome measures were HbA_{1c}, insulin dose, and eGDR (estimate of insulin sensitivity based on waist-to-hip ratio, hypertension, and HbA_{1c}).

RESULTS — LTPA correlated with HbA_{1c} in women ($r = -0.12$, $P = 0.007$) but not in men ($r = -0.03$, $P = 0.592$). Sedentary women had higher HbA_{1c} than moderately active and active women: 8.8 ± 1.4% vs. 8.3 ± 1.4% vs. 8.3 ± 1.4% ($P = 0.004$), whereas HbA_{1c} in men was 8.4 ± 1.3% vs. 8.2 ± 1.4% vs. 8.2 ± 1.3% ($P = 0.774$), respectively. In men, insulin doses were 0.74 ± 0.21 vs. 0.71 ± 0.20 vs. 0.68 ± 0.23 IU · kg^{-1} · 24 h^{-1} ($P = 0.003$). In both sexes, sedentary patients had lower eGDRs than active patients [median (interquartile range) 5.5 (4.0–8.2) vs. 6.8 (4.7–8.8) vs. 6.7 (4.6–8.6) mg · kg^{-1} · min^{-1}; $P < 0.01$ for sedentary vs. others]. Age, obesity, smoking, insulin dose, social class, diabetic nephropathy, or cardiovascular disease did not explain the results.

CONCLUSIONS — Low levels of LTPA were associated with poor glycemic control in type 1 diabetic women. Men seem to use less insulin when physically active. Increased LTPA levels were associated with increased estimated insulin sensitivity. Longitudinal studies are needed to further clarify the effects of LTPA on type 1 diabetes.

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Abbreviations: eGDR, estimated glucose disposal rate; LTPA, leisure time physical activity; MET, metabolic equivalent; UAER, urinary albumin excretion rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Several recent studies have emphasized the importance of physical activity in the prevention of type 2 diabetes (1–4). These studies have shown that progression from the state of impaired glucose tolerance to overt diabetes can be inhibited, or at least postponed, by changing dietary habits and/or increasing the amount of physical activity. In a meta-analysis of 14 studies, exercise resulted in a clinically significant reduction in postintervention HbA_{1c} in type 2 diabetic patients (5). Type 1 diabetic patients present features of peripheral insulin resistance that can be improved by increasing physical activity (6–8), rendering a theoretical basis for exercise to also improve glycemic control in type 1 diabetic patients.

One recent cross-sectional study (9) and several intervention studies in the 1980s (6,7,10–17) failed to show any significant improvements in glycemic control by physical activity in type 1 diabetic patients. Only a few studies have shown a positive effect on glycemic control (18–21). Available studies were, however, limited by small numbers of patients or semiquantitative assessments of physical activity. Therefore, our aim was to investigate the association between leisure time physical activity (LTPA) and glycemic control, insulin dose, and estimated insulin sensitivity in a large cohort of adult type 1 diabetic patients by quantifying physical activity with a detailed and validated questionnaire.

RESEARCH DESIGN AND METHODS

— This is a cross-sectional study involving all type 1 diabetic patients participating in the multicenter, nationwide Finnish Diabetic Nephropathy (FinnDiane) study who completed a validated 12-month questionnaire regarding LTPA. All patients had type 1 diabetes, which was defined as diagnosis of diabetes before 35 years of age, permanent insulin treatment started within 1 year of

diagnosis, and serum C-peptide concentrations <0.20 nmol/l. Patients with end-stage renal disease (hemodialysis or renal transplant) were excluded from the study. A total of 1,030 patients (male/female: 482/548) who both fulfilled these criteria and had available data on physical activity were available in the FinnDiane database at the time of the analyses in March 2004. Of these patients, 624 had normal urinary albumin excretion rate (UAER) and were free from cardiovascular complications (myocardial infarction, coronary artery bypass, limb amputation, peripheral artery bypass, or stroke); these patients are later referred to as patients without complications. Normal UAER was defined as <20 μg/min (overnight collection) or <30 mg/24h in at least two of three consecutive urine collections.

The study protocol was approved by the local ethical committees of the participating centers, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

LTPA was assessed by a previously validated questionnaire from the Kuopio Ischemic Heart Disease Risk Factor Study (22,23), a modification of the Minnesota leisure time activity questionnaire (24) adapted to Finnish conditions based on the Mini-Finland survey (25). Validation was performed in 1,163 Finnish men from the general population (median age, 54 years) with maximum oxygen uptake ($V\text{O}_{2max}$) as the standard method of validation; 12-month LTPA correlated with $V\text{O}_{2max}$ ($r = 0.275$) (22). The questionnaire has previously been used in epidemiological studies (26,27). LTPA, including indoor and outdoor activities, was calculated based on the 21 most common Finnish forms of physical activity (walking, hiking, skiing, running, swimming, etc.). Mean frequency, single-session duration, and intensity (graded 0–3) of LTPA were assessed for the preceding 12 months. For each intensity grade, activity-specific metabolic equivalent (MET) values were used according to the standard procedure for the questionnaire. MET is a widely used unit in exercise research and is defined as the ratio of metabolic rate during activity to the rate at rest (1 MET corresponds to an energy expenditure of 1 kcal · kg^{-1} · h^{-1}). Total amount of LTPA per week was calculated by multiplying time spent on the activities by the intensity index expressed in MET.

Patients were grouped as sedentary (<10 MET h/week), moderately active (10–40 MET h/week), and active (>40 MET h/week). The sedentary patient was defined as performing <2 h of moderate-intensity LTPA (10 MET h; e.g., 2 h of walking with an intensity of 5 MET) per week in accordance to prevailing physical activity recommendations (28). Change in physical activity habits during the last 10 years (reported as decreased markedly/slightly, unchanged, or increased markedly/slightly), frequency of activity in adolescence, and participation in competitive sports were also assessed.

Anthropometric data (weight, height, and waist and hip circumferences) and blood pressure were collected by a trained nurse at all referral centers. Data on smoking, medication, and social class (grouped as unskilled/skilled blue collar, upper/lower white collar, farmers, and others) were also collected in the standard FinnDiane questionnaire. Data on cardiovascular complications and retinopathy were obtained from the physician based on medical records at each referral center. Diabetic nephropathy was defined as present or previous evidence of macroalbuminuria (UAER >30 mg/24 h or >200 μg/min in at least two of three consecutive urine collections).

Estimated glucose disposal rate (eGDR) was calculated by the equation originally developed by Williams et al. (29) for use in type 1 diabetic patients. The equation was modified for use with HbA_{1c} instead of HbA_1 (T. Orchard, M. Walsh, personal communication): 24.4 –12.97 (waist-to-hip ratio) –3.39 (hypertension) –0.60 (HbA_{1c}), where hypertension was assigned 0 or 1 based on blood pressure ≥140/90 and/or antihypertensive medication. This equation gives eGDR as milligrams per kilogram per minute and the estimate correlates well ($r^2 = 0.57$) with values measured with a euglycemic-hyperinsulinemic clamp. The equation was defined in 24 type 1 diabetic patients (male-to-female ratio 12/12) from the Pittsburgh Epidemiology of Diabetes Complications Study, with mean age 35.5 years, BMI 27 kg/m^2, HbA_1 9.9%, and unspecified ethnicity (29).

HbA_{1c} was locally determined at each referral center. Serum C-peptide was measured centrally in our laboratory by radioimmunoassay (Linco Research, St. Charles, MO). UAER was determined in one 24-h or overnight urine collection at a central laboratory by radioimmunoassay (Pharmacia, Uppsala, Sweden). Earlier UAER values and serum lipid values were also obtained from the referral centers.

Calculations were performed with SPSS 11.0 software (SPSS, Chicago, IL). For normally distributed variables, parametric tests (ANCOVA, ANOVA) were used. Otherwise, nonparametric tests (Kruskal-Wallis) or logarithmic transformations were used. For categorical variables, a χ^2 test was used. For between-groups comparisons, *P* values for HbA_{1c} were adjusted by ANCOVA for age, BMI, and insulin dose, whereas *P* values for insulin dose were adjusted for age and BMI. *P* values for eGDR were adjusted for age. Correlations for insulin dose were adjusted for age and BMI, whereas correlations for eGDR were adjusted for age. For correlations, two-tailed *P* values were given. Values are presented as means ± SD or median (interquartile range). $P < 0.05$ indicated statistical significance.

RESULTS — Sedentary patients were more frequently men with greater BMI, decreased serum HDL cholesterol, and a greater prevalence of diabetic nephropathy than patients with greater level of LTPA (Table 1). Sedentary men had larger waist-to-hip ratios than more active men. Age, duration of diabetes, and social class were not associated with levels of LTPA. In men, smoking was clearly associated with LTPA.

Sedentary patients had greater HbA_{1c} than moderately active and active patients: 8.6 ± 1.3% vs. 8.3 ± 1.4% vs. 8.3 ± 1.3%, respectively (sedentary vs. moderately active, $P = 0.009$). However, this association between LTPA and HbA_{1c} was found only in women (Table 2). Patients with diabetic nephropathy had greater HbA_{1c} than patients without nephropathy (8.7 ± 1.3% vs. 8.3 ± 1.3%, $P = 0.002$). Therefore, the association between LTPA and HbA_{1c} could be due to less physical activity in patients with diabetic nephropathy. However, virtually the same results regarding LTPA and HbA_{1c} were found in the subgroup of patients without complications (Table 2).

There was an inverse correlation between LTPA and HbA_{1c} in all women ($r = -0.12$, $P = 0.007$) and in women without complications ($r = -0.14$, $P = 0.008$). In the bottom 50th percentile of LTPA (<20.5 MET h/week), the correlation was stronger in all women ($r =$

Table 1—*Clinical characteristics by level of LTPA*

	Sedentary	Moderately active	Active
Men/women	131/116*	246/322	105/110†
Age (years)	38 ± 11	38 ± 12	37 ± 12
Duration of diabetes (years)	22 ± 12	22 ± 12	22 ± 12
BMI (kg/m^2)	25.6 ± 3.5	25.1 ± 3.4	24.8 ± 3.0†
Waist-to-hip ratio			
Men	0.92 ± 0.07	0.90 ± 0.06	0.91 ± 0.08‡
Women	0.83 ± 0.07	0.82 ± 0.07	0.81 ± 0.08
Systolic blood pressure (mmHg)	133 ± 17	131 ± 16	133 ± 18
Diastolic blood pressure (mmHg)	79 ± 9	78 ± 9	79 ± 10
Serum cholesterol (mmol/l)	4.9 ± 0.9	4.9 ± 0.9	4.8 ± 1.0
Serum HDL cholesterol (mmol/l)	1.56 ± 0.45	1.66 ± 0.42	1.69 ± 0.60†
Diabetic nephropathy (%)	16	11	10‡
Cardiovascular disease (%)	3.3	4.8	4.3
Retinopathy (%, including background)	55	52	50
Current smokers (%)			
Men	33	18	15†
Women	24	20	22
White-collar workers (%)			
Men	30	39	35
Women	32	45	40

Data are means ± SD; n = 1,030. *P = 0.024 men vs. women; †$P < 0.05$ (ANOVA/χ^2 tests); ‡$P < 0.05$ sedentary vs. others.

−0.20, P = 0.001) and in women without complications (r = −0.18, P = 0.016); in the upper 50th percentile, no correlation was found. No correlation between LTPA and HbA_{1c} was found in men (r = −0.03, P = 0.592). Dissecting LTPA into components of mean intensity, frequency, and single-session duration, women with LTPA of low intensity and frequency had greater HbA_{1c} than women with corresponding higher intensity and frequency (Table 3).

Proportions of sedentary versus other patients having poor glycemic control (HbA_{1c} >8.5%) were 55% vs. 39% (P = 0.002) in all women and 49% vs. 35% (P = 0.031) in women without complications. In men, corresponding proportions were 44% vs. 38% (P = 0.238) and 42% vs. 36% (P = 0.319), respectively.

The daily dose of insulin correlated with LTPA in all men (r = −0.12, P = 0.010) and in men without complications (r = −0.13, P = 0.034). Active men had a lower insulin dose than sedentary men (Table 2). In all women, but not in women without complications, the insulin dose correlated with LTPA: r = −0.13 (P = 0.034) vs. r = −0.10 (P = 0.060).

Sedentary vs. moderately active vs. active patients had eGDR [median (interquartile range)] of 5.5 (4.0–8.2) vs. 6.8 (4.7–8.8) vs. 6.7 (4.6–8.6) mg · kg^{-1} · min^{-1} ($P < 0.01$ sedentary vs. moderately active or active) in all patients and 7.1 (4.6–8.5) vs. 7.8 (5.6–9.0) vs. 7.9 (5.9–9.2) mg · kg^{-1} · min^{-1} ($P < 0.01$ sedentary vs. moderately active or active) in patients without complications. Correlations between eGDR and LTPA were r = 0.10 (P = 0.001) in all patients and r = 0.12 (P = 0.003) in patients without complications. No major sex differences were apparent (Table 2).

In patients without complications, women with previous or present participation vs. nonparticipation in competitive sports had present HbA_{1c} of 8.1 ± 1.1% vs. 8.4 ± 1.4% (P = 0.020), whereas in men the corresponding values were 8.3 ± 1.5% vs. 8.1 ± 1.2% (P = 0.188). Frequency of LTPA in adolescence was not associated with present HbA_{1c} (data not shown). The change in LTPA during the last 10 years was also associated with HbA_{1c}. Women reporting a decline in LTPA had higher HbA_{1c} values than those reporting an increase in LTPA (Fig. 1), a result found statistically significant in all women but not in women without complications. For men, no association between changes in LTPA and HbA_{1c} was found (data not shown).

A sedentary level of LTPA, insulin dose (international units per kilogram per 24 h), age, duration of diabetes, BMI, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, antihypertensive medication, serum cholesterol, serum HDL cholesterol, diabetic ne-

Table 2—*HbA_{1c}, insulin dose, and insulin sensitivity by level of LTPA*

	Sedentary	Moderately active	Active	*P*
All patients (n = 1,030)				
HbA_{1c} (%)				
Women	8.8 ± 1.4*	8.3 ± 1.4	8.3 ± 1.4	0.004
Men	8.4 ± 1.3	8.2 ± 1.4	8.2 ± 1.3	0.844
Insulin (IU · kg^{-1} · 24 h^{-1})				
Women	0.71 ± 0.22	0.71 ± 0.23†	0.66 ± 0.22	0.036
Men	0.74 ± 0.21†	0.71 ± 0.20	0.68 ± 0.23	0.003
eGDR (mg · kg^{-1} · min^{-1})				
Women	6.8 (4.6–8.7)†	7.4 (5.3–9.2)	7.3 (5.5–9.2)	0.038
Men	4.7 (3.5–7.4)†	5.4 (3.9–8.1)	5.5 (4.0–8.0)	0.052
Without complications (n = 624)‡				
HbA_{1c} (%)				
Women	8.7 ± 1.4*	8.2 ± 1.3	8.2 ± 1.3	0.042
Men	8.3 ± 1.3	8.1 ± 1.4	8.1 ± 1.2	0.659
Insulin (IU · kg^{-1} · 24 h^{-1})				
Women	0.72 ± 0.20	0.72 ± 0.24	0.67 ± 0.20	0.229
Men	0.76 ± 0.21†	0.74 ± 0.23	0.69 ± 0.23	0.013
eGDR (mg · kg^{-1} · min^{-1})				
Women	8.0 (5.8–9.0)	8.3 (6.2–9.4)	8.5 (6.5–9.7)	0.191
Men	6.0 (4.1–8.2)	7.0 (4.6–8.4)	7.6 (5.1–8.5)	0.090

Data are means ± SD or median (interquartile range). *$P < 0.017$ vs. moderately active; †$P < 0.017$ vs. active; ‡excluding patients with elevated UAER, myocardial infarction, coronary artery bypass, limb amputation, peripheral artery bypass, or stroke.

Table 3—*HbA_{1c} by components of LTPA for patients without complications*

Component	Women	Men
Intensity		
Low	8.8 ± 1.4* (21)	8.1 ± 0.9 (21)
Moderate	8.1 ± 1.2 (66)	8.2 ± 1.4 (43)
High	8.4 ± 1.7 (13)	8.2 ± 1.5 (36)†
P	0.012	0.724
Frequency		
<1 time/week	9.0 ± 1.4‡ (16)	8.3 ± 1.0 (26)
1–2 times/week	8.4 ± 1.3 (23)	8.3 ± 1.1 (30)
>2 times/week	8.2 ± 1.3 (61)	8.1 ± 1.7 (44)§
P	0.008	0.425
Duration		
<3 h/week	8.5 ± 1.4 (36)	8.3 ± 1.3 (42)
3–6 h/week	8.3 ± 1.4 (31)	8.1 ± 1.5 (32)
>6 h/week	8.1 ± 1.3 (33)	8.1 ± 1.2 (26)‖
P	0.156	0.173

Data are means ± SD (%); $n = 624$. Percentages represent distribution of corresponding level of component of LTPA within each sex. *$P = 0.001$ vs. moderate intensity; †$P = 0.001$ vs. women with high LTPA intensity; ‡$P = 0.002$ vs. >2 times/week; §$P = 0.001$ vs. women with LTPA frequency >2 times/week; ‖$P = 0.037$ vs. women with LTPA duration >6 h/week.

phropathy, cardiovascular disease, laser-treated retinopathy, current smoking, and social class were entered in a logistic regression model with poor glycemic control (HbA_{1c} >8.5%) as the dependent variable. In women, a sedentary level of LTPA (odds ratio 2.07 [95% CI 1.18–3.62]), smoking (2.01 [1.11–3.63]) and insulin dose (4.82 [1.31–17.79]) were independently associated with poor glycemic control. In men, low social class was the only independently associated variable (1.91 [1.09–3.36]).

CONCLUSIONS — Physical activity is generally recommended as a crucial component in the management of diabetes (30). It has previously been shown that higher physical activity is associated with lower mortality among type 1 diabetic men (31), but there is no convincing evidence that physical activity has a positive effect on glycemic control in type 1 diabetic patients. In this cross-sectional study of 1,030 Finnish type 1 diabetic patients, we showed that low levels of LTPA were associated with poor glycemic control. The association was also evident in patients with normal renal function and without major cardiovascular complications, indicating that the effect of physical activity was not biased by diabetic complications (i.e., that patients highly affected by their disease perform little physical activity). However, it is of note that the association was found only in women.

In men, on the other hand, we found an association between higher levels of LTPA and lower use of exogenous insulin. This association was less substantial in women because no association was found in women without complications. Therefore, one possible explanation for the observed sex difference in respect to LTPA and HbA_{1c} might be a difference in behavior among men and women in adjusting insulin doses in response to physical activity. Men more often reported high-intensity LTPA; women in turn reported more frequent LTPA than men (Table 3). Diabetic men may tend to decrease insulin doses to prevent hypoglycemic periods during or after high-intensity physical activity, thus avoiding hypoglycemic symptoms but at the same time losing any possible positive effect of physical activity on glycemic control. This statement is merely speculative and based on our cross-sectional data but is supported by data on male athletes with type 1 diabetes showing poor glycemic control despite high physical activity (32). In our study, however, no association between HbA_{1c} and LTPA in men was found despite adjustment for insulin dose. A possible beneficial effect of physical activity on glycemic control could also be diminished by ingestion of extra carbohydrates in association with exercise (33). Unfortunately, dietary habits were not assessed in our study. We found an association between higher LTPA and higher calculated insulin sensitivity in both sexes, which also may contribute to decreased insulin dosage. It should be noted, however, that an estimation of insulin sensitivity (based on waist-to-hip ratio, hypertension, and HbA_{1c}) was used, not a direct measurement. Decreased insulin dose with increased LTPA might also reflect higher noninsulin-mediated glucose uptake in skeletal muscle tissue (34).

The overall effect of LTPA on glycemic control, insulin dose, and estimated insulin sensitivity was not large, as indicated by low linear correlation coefficients. In women, LTPA explained only 1.4% of the total variance in HbA_{1c}, supporting previous findings of the minimal effect of physical activity on glycemic control. However, we found that in the lower range of LTPA, sedentary women had higher mean HbA_{1c} than more active

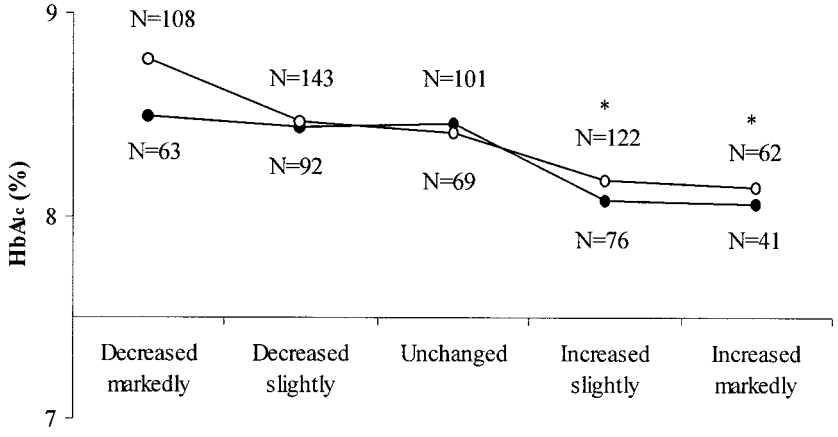

Figure 1—*HbA_{1c} in women by reported change in LTPA during last 10 years. ○, all women; ●, women without complications. *P ≤ 0.01 vs. decreased markedly (all women).*

women, the difference being clinically relevant regarding development of diabetic complications (35). In LTPA subgroups of intensity and frequency, the differences in HbA_{1c} were somewhat more pronounced. A greater proportion of sedentary women also had poor glycemic control compared with nonsedentary women, suggesting that low LTPA may be a risk factor for poor glycemic control. Low LTPA was independently associated with poor glycemic control in a multivariate model. Our data also support that no additional benefit on HbA_{1c} is gained by performing high levels of LTPA. Thus, it seems that avoidance of a sedentary lifestyle is the key message instead of a general dose-response approach to LTPA and glycemic control in type 1 diabetes.

The strength of this study is the large number of patients and the use of a detailed, validated, and quantitative physical activity questionnaire. However, the cross-sectional design of the study somewhat limits the interpretation of the results, and further prospective studies are needed. Several confounding variables could have affected the glycemic control. It should be noted that the effect of LTPA on glycemic control in women could not be explained by age, obesity, insulin dose, diabetic nephropathy, cardiovascular disease, social class, or smoking. The LTPA questionnaire has so far not been validated for women. However, in addition to the total MET hours per week score, it should be appreciated that glycemic control was associated with plain variables such as general frequency and intensity of LTPA (asked directly as "how often?" and "how intense?").

There are many potential benefits from LTPA in patients with type 1 diabetes apart from improvement of glycemic control. However, poor glycemic control increases the risk for microvascular complications in type 1 diabetes (35). It seems that LTPA equal to a weekly dose of <2 h of walking might confer greater risk for poor glycemic control, at least in women. Thus, the clinician should encourage both the type 2 diabetic patient and the type 1 diabetic patient to perform regular LTPA according to present recommendations.

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