Combined Treatment With Exercise Training and Acarbose Improves Metabolic Control and Cardiovascular Risk Factor Profile in Subjects With Mild Type 2 Diabetes

HENRIK WAGNER, MD[1]
MARIE DEGERBLAD, MD[1]
ANDERS THORELL, MD[2]
JONAS NYGREN, MD[2]
AGNETA STÅHLE, PHD[3]
JEANETTE KUHL, MD[1]
TORKEL B. BRISMAR, MD[4]
JOHN ÖHRVIK, PHD[5]
SUAD EFENDIC, MD[1]
PETER N. BÅVENHOLM, MD[6]

OBJECTIVE — The effect of exercise training and acarbose on glycemic control, insulin sensitivity, and phenotype was investigated in mild type 2 diabetes.

RESEARCH DESIGN AND METHODS — Sixty-two men and women with type 2 diabetes were randomized to 12 weeks of structured exercise training with or without acarbose treatment or to acarbose alone. Glycemic control was determined by HbA_{1c} (A1C), insulin sensitivity (M value) by euglycemic-hyperinsulinemic clamp, and regional fat distribution by computerized tomography and dual X-ray absorptiometry. Physical fitness was determined as maximal oxygen uptake (Vo_{2max}). All investigations were performed before and after the intervention.

RESULTS — Forty-eight subjects completed the study. Exercise improved M value by 92% ($P = 0.017$) and decreased total and truncal fat ($P = 0.002$, 0.001) and systolic blood pressure ($P = 0.01$) but had no significant effect on Vo_{2max} or A1C level. The combination of exercise and acarbose significantly decreased fasting plasma glucose, A1C, lipids, and diastolic blood pressure and increased Vo_{2max}, whereas effects on M value and body composition were comparable with that of exercise alone. Acarbose alone had no significant effect on either M value or A1C but decreased systolic ($P = 0.001$) and diastolic blood pressure ($P = 0.001$) and fasting proinsulin level ($P = 0.009$). Multiple regression analysis showed that addition of acarbose to exercise improved glycemic control.

CONCLUSIONS — In subjects with mild type 2 diabetes, exercise training improved insulin sensitivity but had no effect on glycemic control. The addition of acarbose to exercise, however, was associated with significant improvement of glycemic control and possibly cardiovascular risk factors.

Diabetes Care 29:1471–1477, 2006

From the [1]Department of Molecular Medicine and Surgery, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; the [2]Department of Surgery, Ersta Hospital, Karolinska Institutet, Stockholm, Sweden; [3]Neurotec, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; the [4]Department of Diagnostic Radiology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; the [5]Department of Medical Epidemiology and Biostatistics, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; and the [6]Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden.

Address correspondence and reprint requests to Henrik Wagner, Department of Molecular Medicine and Surgery, Karolinska Institutet, SE-171 76 Stockholm, Sweden. E-mail: henrik.wagner@karolinska.se.

Received for publication 21 December 2005 and accepted in revised form 29 March 2006.

S.E. and P.N.B. have been members of an advisory board for and have received honoraria and grant/research support from Bayer.

Abbreviations: apo, apolipoprotein; CVD, cardiovascular disease; PAI-1, plasminogen activator inhibitor-1.

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

DOI: 10.2337/dc05-2513

It is well established that not only manifest type 2 diabetes but also impaired glucose tolerance and impaired fasting glucose constitute a significant risk for development of cardiovascular disease (CVD) (1). This risk can partly be explained by a concomitant high prevalence of traditional CVD risk factors, such as obesity, hypertension, insulin resistance, and dyslipidemia. However, the role of hyperglycemia per se, particularly postprandial hyperglycemia, in exacerbation of CVD has been demonstrated in both epidemiological and clinical studies (2,3). Accordingly, in the therapy of type 2 diabetes, advocated regimes focus on correcting traditional CVD risk factors and normalizing glycemia. Regular exercise training is perceived as a cornerstone of diabetes therapy, although the effect on HbA_{1c} (A1C) level is poorly documented in patients with mild hyperglycemia (4,5). Therefore, the main objective in the present study was to investigate, in patients with type 2 diabetes and mild hyperglycemia, the impact of structured moderate- to high-intensity exercise training alone or in combination with acarbose treatment on glycemic control, phenotype characteristics, and cardiovascular risk factor profile. In addition, we randomized patients to acarbose alone. Acarbose was chosen as treatment since the compound is safe, reduces postprandial glycemia, and improves β-cell responsiveness (6,7). Furthermore, it has been reported that acarbose increases (8,9), or has no effect on (7,10–12), insulin sensitivity.

RESEARCH DESIGN AND METHODS

— The subjects were recruited from referrals to our diabetes outpatient daycare unit and by advertising in local newspapers. Ninety-four Swedish subjects were screened, of which 32 were not included in the study due to either failure to meet the inclusion criteria or unwillingness to adhere to the protocol. Thus, 62 subjects (17 women and 45

Table 1—*Basic characteristics of study population*

	Exercise			Exercise + acarbose		
n	17			14		
n (male/female)	14/3			8/6		
Age/diabetes duration (years)	54 (50–58)/4 (2–5)			57 (52–58)/3.5 (1–6)		
n treatment at screening (diet/metformin/sulfonylurea)	6/4/7			7/4/3		
n (antihypertensive/lipid-lowering treatment)	7/2			6/2		
	Before	After	*P*	Before	After	*P*
BMI (kg/m^2)	28.7 (25.6–30.3)	28.4 (25.1–29.2)	0.010	28.7 (26.3–29.6)	27.6 (25.7–28.5)	0.004
Waist circumference (cm)	99 (95–106)	99 (92–105)	0.036	103 (99–107)	100 (95–104)	0.008
Lean body weight (DXA) (kg)	60.5 (55.3–64.3)	60.5 (56.9–65.2)	NS	53.1 (41.1–72.1)	53.3 (42.3–71.7)	NS
Total fat (DXA) (kg)	21.7 (17.2–26.5)	19.3 (15.3–24.6)	0.002	23.0 (18.8–31.2)	20.5 (17.8–29.2)	0.001
Truncal fat (DXA) (kg)	11.9 (9.3–13.9)	11.0 (8.7–13.1)	0.001	12.4 (10.4–16.4)	10.6 (9.7–14.4)	0.004
Total abdominal fat area CT (cm^2)	454 (321–504)	406 (358–471)	0.015	455 (353–518)	403 (318–470)	0.002
Intra-abdominal fat area CT (cm^2)	252 (158–319)	258 (130–284)	0.035§	244 (202–292)	222 (154–263)	0.009
Maximal workload (W)	210 (190–250)	230 (210–270)	0.005	190 (135–230)	190 (150–250)	0.028
Vo_{2max}/lean weight(ml · min^{-1} · kg^{-1})	42.7 (39.6–47.5)	46.0 (41.5–47.6)	0.093	39.7 (36.2–41.6)	44.2 (38.0–46.6)	0.046
Fasting blood glucose (mmol/l)	7.8 (7.5–9.0)	7.4 (6.7–8.5)	NS	6.7 (5.9–9.5)	6.4 (5.7–7.7)	0.048
A1C (%)	6.6 (6.1–7.1)	6.1 (5.7–6.6)	0.102	5.9 (5.1–6.6)	5.5 (5.0–5.9)	0.002
Fasting insulin (pmol/l)	84 (69–111)	84 (72–102)	NS	89 (66–108)	86 (72–99)	NS
Fasting proinsulin (pmol/l)	22.1 (14.9–26.2)	21.2 (15.0–25.1)	NS	20.7 (11.6–26.6)	15.7 (8.6–22.9)	0.013
Insulin clamp (pmol/l)	429 (369–453)	446 (368–509)	NS	425 (366–495)	390 (341–477)	NS
M value/lean weight(mg · min^{-1} · kg^{-1})	5.1 (3.9–7.2)	9.8 (4.3–10.3)	0.017	6.1 (3.5–9.3)	9.5 (6.7–13.9)	0.002

Data are median (lower–upper quartile). Wilcoxon signed-rank test was used within each group. Kruskal-Wallis ANOVA was used to test differences between groups. Wilcoxon rank-sum test was used for post hoc analysis. Multiple regression analysis was used to adjust for sex. All *P* values are listed for the Kruskal-Wallis ANOVA, otherwise if <0.2. *P* values >0.2 are listed as not significant (NS). *Exercise + acarbose vs. acarbose; †exercise vs. acarbose; ‡exercise vs. exercise + acarbose. §*P* value reflects a decrease. DXA, dual-energy X-ray absorptiometry.

men) with type 2 diabetes were included in the study. The patients' diagnosis was established at least 3 months before inclusion. Subjects who had an A1C <7.5% (normal reference <5.2%), were aged 45–60 years, and had a BMI 25–30 kg/m^2 at the start of the wash-out period were eligible for the study. At randomization, patients who had an A1C >8.5% were excluded. The median duration of diabetes was 3 years. Three individuals had a history of cardiovascular complications (coronary bypass surgery and two cerebral transient ischemic attacks). One-third of the participants had microalbuminuria. All subjects were on diet treatment. A majority of the participants (60%) was also on one oral antidiabetic drug before entering the study, whereas 38% were on antihypertensive and 15% on lipid-lowering treatment (Table 1). None of the study subjects had previously participated in any regular exercise program with more than one training session per week. All participants were instructed to maintain their lifestyle habits throughout the course of the study.

Following a wash-out period of antidiabetic medication for at least 6 weeks, the participants were randomized to one of three intervention groups: *1*) twelve weeks of aerobic/anaerobic exercise group training for 50 min three times per week (no placebo was given), *2*) twelve weeks of exercise (as in *1*) and acarbose treatment (as in *3*), and *3*) twelve weeks of treatment with acarbose alone. The target dose of acarbose was 100 mg three times daily to be taken with major meals. The dose was uptitrated during the first 4 weeks of intervention. If gastrointestinal side-effects occurred, the titration period was prolonged and/or the target dose reduced. Pill count was performed and acceptable compliance per protocol defined as 75–120%. All participants received written and oral information regarding the nature and potential risks of the study and gave their informed consent. The experimental protocol was approved by the ethics committee at the Karolinska University Hospital.

Hyperinsulinemic-euglycemic clamp

This investigation was performed at the research units at the Karolinska University and Ersta Hospitals. The patients had a light standardized meal at 10 P.M. in the evening, and after an overnight fast the investigation was performed at 8 A.M. After 12 weeks of intervention, the insulin clamp studies were repeated and performed 24–36 h after the last bout of exercise for subjects in groups 1 and 2. Insulin (Actrapid; Novo Nordisk, Copenhagen, Denmark) was infused at 1.0 mU · kg^{-1} · min^{-1} for 120 min. Glucose (200 mg/ml) was simultaneously infused intravenously at a variable rate to maintain the blood glucose concentration stable at 5.0 mmol/l (13). In four clamps in four different subjects, a steady-state period at the targeted blood glucose level was not reached within 120 min. These investigations were prolonged 20–30 min in order to obtain a steady state.

Body composition and physical fitness

Computerized tomography and dual X-ray absorptiometry were used to determine abdominal fat area and body fat mass, respectively (14). Maximal workload and Vo_{2max} were assessed during an

Table 1—Continued

Acarbose								
17								
13/4								
54 (49–58)/3 (2–5)								
6/8/3								
5/3								
			ANOVA			ANOVA		
Before	After	*P*	*P* overall	*P* post hoc		Adjusted for sex		
27.4 (25.7–28.6)	26.8 (26.4–28.1)	NS	0.035	0.029*		0.007*	0.184†	0.132‡
100 (97–104)	99 (97–103)	0.055	0.109			0.029*	0.177‡	
54.6 (49.3–61.5)	55.3 (48.1–60.5)	NS	0.651					
23.0 (21.1–27.0)	22.2 (19.2–25.2)	0.177	0.140			0.051*	0.177†	
12.1 (10.8–13.8)	11.8 (9.9–13.1)	0.193	0.235			0.151*		
426 (345–484)	402 (343–471)	0.093	0.118			0.018*	0.075‡	
227 (173–261)	205 (183–273)	NS	0.309			0.052*		
190 (170–210)	190 (165–210)	NS	0.001	0.035*	0.005†	0.006*	0.003†	
42.3 (40.6–45.0)	43.1 (38.9–44.1)	0.102	0.015	0.021*	0.089†	0.001*	0.034†	0.120‡
7.3 (6.4–7.8)	6.8 (6.5–7.9)	NS	0.315			0.023*	0.071‡	
5.8 (5.1–6.6)	5.2 (5.0–6.8)	0.173	0.253			0.032*	0.043‡	
96 (69–108)	96 (78–108)	NS	0.816					
26.9 (15.3–44.1)	16.7 (12.4–27.1)	0.009	0.382			0.157‡		
428 (387–486)	426 (368–512)	0.163	0.675					
6.9 (6.3–10.2)	6.4 (3.8–9.0)	0.163	0.002	0.007*	0.005†	0.002*	0.003†	

exercise test performed on an electrically braked bicycle ergometer (14). These investigations were performed at the Karolinska University Hospital and within a week after the clamp investigation.

Exercise intervention

Allocated subjects participated in a combined aerobic and dynamic strength training group program at the Karolinska University Hospital. The training program consisted of a warm-up period for 6 min and was followed by 3- to 4-min periods of running, flexibility movements, and dynamic strength training of extremities, abdomen, and back, with the weight of the own body as counterweight. Stretching and cool down terminated the session. A specialized senior physiotherapist led and supervised each training session. To increase the adherence to training, five training sessions at different times during the week were offered.

Two exercise targets were used: *1*) an individual exercise intensity of ≥50% of maximal exercise capacity, based on the maximal heart rate reached during the baseline exercise test, during at least 40 min (15) and *2*) ≥80% during three heavier periods of 3–4 min, engaging large muscle groups for training of central circulation (15).

The design of the training protocol included adjustment of the workload as the subjects became trained during the 12-week period. First, the intensity during the training program was individually adjusted and based on the performance at the baseline exercise test. The subjects were encouraged to reach an exertion of 13–15/20 rated on Borg's Rated Perceived Exertion scale during the heavier parts of the training program and 9–11/20 during the rest of the program (16). Second, to ascertain that the targeted individual exercise intensity was reached during the heavier parts of the sessions, a new computed online heart rate recording system was used (Activio, Stockholm, Sweden). The heart rate was assessed at one of the three weekly training sessions during weeks 1, 6, and 12 of the training period. At the same time points, the subjects also rated their perceived exertion using the Rated Perceived Exertion scale during the heavier parts of the session.

Plasma analyses

Blood glucose was determined by a glucose oxidase method. Plasma insulin was determined by radioimmunoassay, for which cross-reactivity with proinsulin was 100%, and the intra- and interassay coefficient of variation (CV) <3.1% and <3.9%, respectively. Plasma proinsulin was measured by a commercial radioimmunoassay kit (intra- and interassay CV 2.0% and 5.0%, respectively), with a cross-reactivity for insulin and C-peptide <0.1%. A1C was analyzed using the high-performance liquid chromatography Mono-S method (intra- and interassay CV 0.48% and 2.67%, respectively), which gives absolute values ~0.9 lower than the Diabetes Control and Complications Trial reference method. Plasminogen activator inhibitor-1 (PAI-1) concentration was measured by a commercial enzyme-linked immunosorbent assay kit.

Statistical analyses

All continuous variables are presented as median (lower-upper quartile). Due to small sample size, stratification for, for example, A1C was not performed. Therefore, analyses were made on relative and not absolute differences, and all continuous variables were log transformed before analysis. Wilcoxon signed-rank test was used to test for within-group differences. Kruskal-Wallis nonparametric ANOVA test was used to test for differences of relative changes between groups. Wilcoxon's rank-sum test was used for pairwise comparisons between groups when the

Table 2—*Blood pressure and lipids*

	Exercise (n = 17)			Acarbose + exercise (n = 14)		
	Before	After	P	Before	After	P
Blood pressure systolic (mmHg)	140 (135–150)	135 (120–140)	0.010	145 (140–155)	130 (120–135)	0.001
Blood pressure diastolic (mmHg)	82.5 (75–87.5)	75 (75–80)	0.155	82.5 (75–95)	75 (75–80)	0.021
Total cholesterol (mmol/l)	4.8 (4.7–5.3)	4.7 (4.4–5.3)	0.179	5.0 (4.5–5.4)	4.9 (4.3–5.1)	0.039
LDL cholesterol (mmol/l)	3.2 (2.9–3.7)	3.1 (2.9–3.4)	NS	3.2 (2.8–3.6)	3.2 (2.9–3.4)	NS
HDL cholesterol (mmol/l)	1.0 (1.0–1.1)	1.0 (0.9–1.0)	NS	1.1 (0.9–1.3)	1.1 (0.9–1.2)	0.093
Triglycerides (mmol/l)	1.4 (1.2–1.9)	1.0 (0.7–1.8)	0.093	1.4 (0.9–1.8)	1.0 (0.7–1.4)	0.004
ApoA1 (g/l)	1.37 (1.19–1.49)	1.34 (1.32–1.46)	NS	1.44 (1.27–1.60)	1.32 (1.22–1.48)	0.109
ApoB (g/l)	1.11 (1.02–1.20)	1.03 (0.92–1.11)	0.049	1.08 (1.04–1.16)	1.01 (0.92–1.14)	0.035
ApoB-to-apoA1 ratio	0.80 (0.71–0.87)	0.72 (0.61–0.83)	0.003	0.83 (0.64–0.86)	0.77 (0.64–0.88)	NS
PAI-1 (kIU/l)	25 (12–34)	25 (18–30)	NS	22 (16–37)	20 (4.4–28)	0.028

Data are median (lower-upper quartile). Wilcoxon signed-rank test was used within each group. Kruskal-Wallis ANOVA was used to test differences between groups. Wilcoxon rank-sum test was used for post hoc analysis. Multiple regression analysis was used to adjust for sex. All P values are listed for the Kruskal-Wallis ANOVA, otherwise if <0.2. P values >0.2 are listed as not significant (NS). *Exercise + acarbose vs. acarbose; †exercise vs. exercise + acarbose; ‡exercise vs. acarbose.

overall ANOVA was significant. Multiple regression analysis was performed to adjust for age, sex, and A1C at baseline, if necessary. Statistical significance was set at $P < 0.05$ two sided. No adjustment for multiple testing was performed. Data processing was performed using STATISTICA, StatSoft (version 7.1).

RESULTS

Study population

Of 62 included subjects, a total of 14 (4 women and 10 men) were excluded from the final analysis. Five subjects discontinued the study due to dissatisfaction with the allocated intervention or lack of time to participate. Seven subjects (one in the exercise group, five in the combined treated group, and one in the acarbose group) were excluded from analysis due to noncompliance (<60% attended training sessions, pill count <75% or >120%, or absent). Finally, two subjects were excluded during the course of the study due to arthritis and deep vein thrombosis. Thus, 48 participants were eligible for the final analysis.

Basic characteristics

In total, the subjects were middle aged (median age 55.5 years) and overweight (BMI 27.7 kg/m^2) with an increased abdominal obesity, as reflected by an increased waist circumference (100 cm). There was an unbalance in sex distribution, since 43% of the participants in the combined treated group were women compared with 17 and 23% in the acarbose and exercise group, respectively. There were no differences in age distribution between the three groups (Table 1). The participants had moderately increased A1C level (6.2%) and fasting blood glucose concentration (7.5 mmol/l). Total plasma cholesterol (5.0 mmol/l), LDL cholesterol (3.3 mmol/l), and triglyceride levels (1.5 mmol/l) were above present recommendations, whereas HDL cholesterol level (1.1 mmol/l) were below (17).

Compliance with the exercise intervention was 86 and 84% in the exercise and the combined treated group, respectively, and compliance with acarbose treatment was 95 and 96% in the acarbose and the combined treated group, respectively. Accordingly, there were no group differences in this respect.

Effects of treatment regimes on phenotype characteristics, glycemic control, and insulin sensitivity (Table 1)

Physical training alone during 12 weeks resulted in significant reductions of BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area. Maximal workload was significantly increased (10%, $P = 0.005$), whereas $V_{O_{2max}}$ was unchanged. The M value markedly increased (92%, $P = 0.017$), whereas no significant effect on glycemic control (A1C) was observed.

In the group combining exercise training and acarbose treatment, a significant decrease in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area was observed. Maximal workload and $V_{O_{2max}}$ were significantly increased ($P = 0.028$ and 0.046, respectively). In addition, fasting plasma proinsulin level was significantly reduced (20.7–15.7 pmol/l, $P = 0.013$). Insulin sensitivity (M value) increased by 56% ($P = 0.002$), which remained significant after adjustment for baseline A1C levels and sex. Glycemic control was significantly improved by the combined treatment, as reflected by lowering of fasting blood glucose concentration and A1C level.

Acarbose treatment alone had no effect on A1C level, fasting plasma glucose, M value, BMI, body composition, or $V_{O_{2max}}$. Fasting plasma proinsulin level was significantly reduced as a result of acarbose treatment (26.9–16.7 pmol/l, $P = 0.009$).

Insulin level during clamps (steady state) did not differ within or among the three different intervention groups.

Effects of treatment regimes on lipids and apolipoprotein levels, plasminogen activator inhibitor 1 level and blood pressure (Table 2)

Physical training alone did not influence lipid or PAI-1 levels. However, apolipoprotein (apo) B–to–apoA1 ratio was significantly decreased (0.80–0.72, $P = 0.003$), suggesting an overall improved lipid profile. A significant decrease in systolic blood pressure (140–135 mmHg, $P = 0.010$) was observed but not in diastolic blood pressure (82.5–75 mmHg, $P = 0.155$).

The combined treatment with exercise and acarbose resulted in a significant decrease in total cholesterol (5.0–4.9 mmol/l, $P = 0.039$), total triglycerides (1.4–1.0 mmol/l, $P = 0.004$), and apoB levels (1.08–1.01, $P = 0.035$). LDL and HDL cholesterol were unchanged. PAI-1 and blood pressure levels were signifi-

Table 2—*Continued*

Acarbose (n = 17)			ANOVA			ANOVA		
Before	After	P	P overall	P post hoc		Adjusted for sex		
145 (135–155)	130 (120–140)	0.001	0.271			0.111*	0.055†	
85 (80–90)	80 (70–85)	0.001	0.439			0.133‡	0.071†	
5.6 (4.8–6.1)	5.2 (4.5–5.7)	NS	0.670					
3.5 (3.0–4.0)	3.7 (3.1–4.0)	NS	0.455					
1.0 (0.9–1.2)	1.0 (0.8–1.1)	0.041	0.186					
1.6 (1.0–2.4)	1.4 (1.0–1.9)	0.059	0.346			0.187*		
1.44 (1.28–1.62)	1.36 (1.22–1.50)	0.102	0.100			0.087‡	0.112†	
1.21 (1.01–1.31)	1.17 (1.08–1.32)	NS	0.091			0.174*	0.152‡	
0.88 (0.67–0.98)	0.89 (0.80–1.01)	0.136	0.004	0.003‡	0.163†	0.125*	0.001‡	0.090†
21 (11–30)	20 (11–42)	NS	0.205			0.085*	0.083†	

cantly decreased by the combined treatment regime.

Acarbose treatment alone resulted in a small decrease in plasma HDL level, whereas no changes in other lipids or apolipoprotein levels were observed. PAI-1 level were not changed, whereas both diastolic and systolic blood pressures were decreased.

Comparisons of treatment regimes

Multiple regression analysis was used for comparisons of treatment regimes (Tables 1 and 2). In the whole study population, the relative decrease in A1C level was significantly higher in men ($P = 0.03$, data not shown). After adjustment for impact of sex in the three groups, A1C level was decreased when acarbose was added to exercise ($P = 0.043$). Moreover, this regime resulted in a nearly significant decrease in fasting plasma glucose concentration ($P = 0.071$), systolic ($P = 0.055$) and diastolic ($P = 0.071$) blood pressure, total fat area ($P = 0.075$), apoB-to-apoA ratio ($P = 0.090$), and PAI-1 level ($P = 0.083$).

CONCLUSIONS — In patients with mild type 2 diabetes, 12 weeks of moderate to high combined aerobic and dynamic strength training increased insulin sensitivity and improved body composition as well as systolic blood pressure but had no significant effect on glycemic control. Importantly, when exercise training was combined with acarbose treatment (median dose 245 mg/day), glycemic control was significantly improved as reflected by a decrease in A1C level and fasting plasma glucose concentration. In addition, the overall cardiovascular risk factor profile was improved. Treatment with acarbose alone was associated with improvement in blood pressure and β-cell function, as reflected by a significant decrease in plasma proinsulin level. Although the median fo A1C was decreased by 0.6%, the difference was not significant.

Results from studies investigating the impact of exercise on glycemic control in patients with type 2 diabetes are inconsistent and often limited by small sample sizes. Similarly, in the present study, the number of patients in each group was rather small and the group on exercise training alone did not receive placebo. Importantly, Boulé et al. (4) reported a meta-analysis in 2001 including all relevant randomized clinical trials in adults with type 2 diabetes that comprised structured exercise training with a duration of ≥8 weeks. It demonstrated that the effect of exercise interventions on the weighted mean postintervention A1C level was 0.66%, similar to the present findings. The effect of exercise on glycemic control tended to be more pronounced in patients with high A1C level at study inclusion. In the three studies that included participants with A1C level of ~7.5% (similar to level in the present study), exercise was without effect on glycemic control. In a more recent meta-analysis, Boulé et al. (18) describes a relationship between exercise volume (total weekly energy expenditure) and changes in cardiorespiratory fitness and A1C. Interventions using higher aerobic exercise intensities produced not only larger improvement in $V\text{O}_{2max}$ but also in glycemic control. The study using the highest exercise intensity (45 min of cycling at 75% of $V\text{O}_{2max}$ two times per week plus an intermittent exercise session one time per week during 2 months), showed the greatest improvement in A1C (from 7.9 to 6.4%) (19). However, exercise interventions at high intensity may be hazardous and should generally not be recommended to sedentary people with type 2 diabetes without preceding medical evaluation (20).

In the present study, a structured combined aerobic and dynamic strength training group program of moderate to high intensity was used. Sex and baseline A1C levels may influence the outcome of the interventions; therefore, adjustments for these variables were performed. Insulin sensitivity was measured using a standard hyperinsulinemic-euglycemic clamp technique. Insulin levels during the clamps were comparable in the three groups studied and leveled at ~430 pmol/l. This implies that hepatic glucose production was suppressed and glucose uptake occurred primarily in muscle and fat. Despite a remarkable increase in insulin sensitivity (92% increase in M value) and an increase in maximal workload, exercise per se did not significantly improve $V\text{O}_{2max}$ or A1C level. Since we have ascertained that the targeted individual exercise intensity was reached, we conclude that moderate to high intensity exercise alone was not sufficient to significantly improve glycemic control or $V\text{O}_{2max}$ in subjects who had only a modest increase in pretraining A1C level. Of note, when exercise training was combined with acarbose treatment, the $V\text{O}_{2max}$ was significantly increased.

To optimize the glycemic control in patients with type 2 diabetes, beyond what is achievable with exercise training alone, addition of an oral antidiabetic medication is an option. In the present study, acarbose, alone or in combination with exercise, was chosen as a glucose-lowering agent for several reasons. First, acarbose is an α-glycosidase inhibitor that improves glycemia by delaying absorption of complex carbohydrates in the gastrointestinal tract and poses no risk of

provoking hypoglycemia. Second, epidemiological studies (2,21–23) suggest that postprandial hyperglycemia is a stronger cardiovascular risk than fasting hyperglycemia. Third, acarbose, by reducing postprandial hyperglycemia, positively affects a number of CVD risk factors, including dysglycemia, oxidative stress, endothelial dysfunction, dyslipidemia, and hypercoagulability (24). It has also been proposed that acarbose treatment enhances the release of the incretine hormone glucagon-like peptide-1 (25), which is known to enhance β-cell responsiveness and suppress glucagon release and prolong transit time of nutrients in the gastrointestinal tract resulting in both improved postprandial glycemia and insulin sensitivity (6,7). Finally, the results from clinical studies suggest that acarbose is associated with significant cardiovascular benefits in subjects with impaired glucose tolerance (3) and in people across the diabetes continuum (26). In keeping with these notions, patients receiving acarbose treatment in the present study, alone or in combination with exercise, improved their overall cardiovascular risk profile. Acarbose therapy, when added to exercise training, significantly improved glycemic control. In patients receiving acarbose treatment, there was a significant decrease in proinsulin level, suggesting that the β-cell function was improved. Improvements of insulin secretion and reductions of proinsulin level by acarbose treatment have also been demonstrated by others (27–29). Furthermore, significant reductions in blood pressure, total cholesterol, and triglyceride concentrations, total fat mass, and PAI-1 level were noted in subjects when acarbose treatment was combined with exercise. Thus, our data indicate that acarbose treatment added to exercise improves glycemic control in subjects with mild type 2 diabetes and attenuates cardiovascular risk factors more than is achievable by exercise training alone. Approximately half of all diabetes patients in Sweden are on diet or oral agent treatment and have A1C levels $< 6.5\%$ (30). Thus, the present study population is fairly representative for patients with diabetes in Sweden.

In conclusion, exercise training alone, or acarbose treatment alone, improves cardiovascular risk factor profile in people with type 2 diabetes and mild hyperglycemia, without significant improvement in glycemic control. When acarbose treatment and exercise are combined, glycemic control is significantly improved. Furthermore, the cardiovascular risk factor profile is possibly improved beyond what is achieved with exercise or acarbose alone.

Acknowledgments— This work was supported by the Swedish Medical Research Council (K99-72X00034-35A) and by an unrestrictive grant from Bayer HealthCare.

The authors express their appreciation to the nurses Kajsa Sundquist and Bodil Ljungström at Karolinska Hospital and Ann-Sofie Andersson, Ami Bylund, and Nina Blommé at Ersta Hospital for their performance in the experiments and logistics; to the physiotherapists supervising the training; to the personnel at the laboratory who performed the hormone measurements, as well as the personnel at the Radiology Department and Clinical Research Center; and finally to all volunteers for their participation in the study.

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