Table G3.A14. Summary of Individual Diabetes Exercise/Physical Activity Studies for Treatment of Diabetic Neuropathy, Nephropathy, or Retinopathy That Were Not Both Randomized and Controlled (Note: No Studies Were Both Randomized and Controlled)

Author, Journal, Year (Type of Microvascular Complication, e.g., Neuropathy, Nephropathy, or Retinopathy)	N	Random/Control	Intervention/Measures	Finding
Bernbaum M Diabetes Care 1989 (1) (retinopathy)	N = 47 (28 T1D and 19 T2D) with visual impairment due to DM	Pre-post assessment in subjects with severe visual impairment (10 completely blind, 9 with solely light perception, and 8 legally blind)	Intervention: Exercise 30-45 minutes 3x/week with maximum change in BP 50 mm Hg and maximal BP maintained ≤200 mm Hg Measures: HbA1c, insulin requirements, fasting glucose, weight, BMI, psychological function, serum total, HDL, and LDL cholesterol.	↓ HbA1c from 12.3 to 11.4% and ↓insulin requirements (*P* <0.05 for both) Improved psychological function by Zung Depression Scale, Rosenberg Self-Esteem Scale, and Rand Mental Health Index (*P* <0.05) No change in other measures No vitreous hemorrhage or vision loss reported with temporal association to exercise
Hotta O Nephron 1991 (2) (nephropathy)	53 non-obese males newly diagnosed with T2D and urine malb <30 mg/day	Pre-post intervention	Intervention: 3 weeks of exercise (40-60% VO_{2max} x 20 minutes two times per day) AND low calorie diet x 3 weeks (IBW x 25 kcal/day) Measures: 75 g OGTT, BP, urine albumin, U-B2MG, GFR, RPF	↓ nephropathy from 19.4 to 10.1 mg/day (*P* <0.01) Improved glucose control (fasting glucose from 123.3 to 91.7 (*P* <0.05) and OGTT improved from 238.3 to 151.7 (*P* <0.05) ↓ SBP from 128.4 to 106.4 and ↓DBP from 78.2 to 66.0 (*P* <0.01 for both). No change in U-B2MG, GFR, RPF, or FF
Cruickshanks KJ Ophthalmology 1995 (3) (retinopathy) (See also cited in Table G3.A1. with respect to retinopathy prevention; this table only assesses treatment issues.)	606 with DM diagnosed <30 and without proliferative retinopathy at 1984-1986 exam (those with non-proliferative retinopathy were included)	Prospective Cohort analysis of Wisconsin Epidemiologic Study of Diabetic Retinopathy from entry (1984-1986) to 6-year follow-up (1990-1992)	Intervention: None Measures: Presence and severity of retinopathy (standardized 4-tier scale), progression defined as increase of two tiers on scale Current physical activity by interviewer-standardized questionnaire, historical physical activity as defined by high school/college team sports	No difference in retinopathy progression in either sex with respect to any of the following physical activity measures: Self-rated activity (strenuous vs. sedentary) Blocks walked daily Stairs climbed daily Sweat activity Sports participation in either past week or past year Calculated current energy expenditure Historical participation in team sports Disparate results from 1992 cross-sectional study possibly due to socio-economic or other bias in the cross-sectional study No risk for increased incidence or progression of retinopathy in 32 weight lifters (vitreous hemorrhage incidence was not assessed)

Table G3.A14. Summary of Individual Diabetes Exercise/Physical Activity Studies for Treatment of Diabetic Neuropathy, Nephropathy, or Retinopathy That Were Not Both Randomized and Controlled (Note: No Studies Were Both Randomized and Controlled) (continued)

Author, Journal, Year (Type of Microvascular Complication, e.g., Neuropathy, Nephropathy, or Retinopathy)	N	Random/Control	Intervention/Measures	Finding
Colberg SR J Diabetes Complications 2002 (4) (ulcer prevention, subjects without severe neuropathy but those with mild neuropathy by quantitative somatosensory testing were included)	35 male and female subjects stratified by habitual PA and DM status	Cross-sectional Population representative 4 groups: Control exercise, Control sedentary, DM exercise, DM sedentary. Physical activity stratified as "Exercisers"(≥30/week x 3) or Sedentary" (no routine exercise)	Intervention: None Measures: Cutaneous blood flow to dorsal foot at rest, with ischemic reperfusion (IRP, after cuff occlusion to 40 mm > SBP * 5 min), and with heat exposure to promote thermal vasodilation	DM exercise superior to DM sedentary for cutaneous blood flow to foot during both rest and IRP (P <0.05). No differences between DM exercise and Control sedentary under all conditions measured Control exercise superior to DM sedentary for rest, IRP, and heat (P <0.05) but only superior to DM exercise for heat (P <0.05). No differences in dorsal foot interstitial NO levels between the 4 groups Note: Significant HbA1c and TG difference between DM groups (DM exercise HBA1c: 6.5 ± 0.3 vs. DM sedentary HbA1c: 8.9 ± 0.5; DM exercise TG: 1.53 ± 0.27 mmol/L vs. DM sedentary TG: 3.84 ± 1.26 mmol/L, P <0.05 for both) and more males in DM sedentary (P = NS) but BP, total cholesterol/LDL, BMI, and weight not significantly between DM exercise and DM sedentary.

Table G3.A14. Summary of Individual Diabetes Exercise/Physical Activity Studies for Treatment of Diabetic Neuropathy, Nephropathy, or Retinopathy That Were Not Both Randomized and Controlled (Note: No Studies Were Both Randomized and Controlled) (continued)

Author, Journal, Year (Type of Microvascular Complication, e.g., Neuropathy, Nephropathy, or Retinopathy)	N	Random/Control	Intervention/Measures	Finding
Colberg SR Diabetes Care 2003 (5) (ulcer prevention, subjects without severe neuropathy)	32 T2D and 26 control male and female subjects stratified by habitual physical activity status	Cross-sectional population representative AND pre-post analysis after maximal exercise test 4 groups: Control exercise, Control sedentary, DM exercise, and DM sedentary with same criteria as Colberg 2002 above	Intervention: single maximal exercise test (ETT) Measures: Cutaneous blood flow to dorsal foot at rest and after heat exposure to promote thermal vasodilation; measures performed pre- and post-exercise	No differences between any groups in cutaneous perfusion at baseline in resting state. DM exercise significantly ↑ perfusion after ETT with respect to DM exercise baseline (14.08 ± 2.92 vs. 6.92 ± 2.70, *P* <0.05), while the 3 other groups had non-significant increases in perfusion. After thermal vasodilation to foot in resting pre-exercise state, both non-DM groups had ↑ cutaneous perfusion than both DM groups (*P* <0.05) When measured within 10 minutes post-exercise, Control exercise had ↑ perfusion with respect to DM sedentary (*P* <0.05) but no significant differences between the Control exercise, Control sedentary, and DM sedentary groups were found. Note: DM sedentary and DM exercise groups had comparable HbA1c levels in this study (6.9% and 6.7%, respectively, with both control groups having A1c of 5.7% significantly lower than both DM groups (*P* <0.05). Comparable age, BP, and BMI between groups.
Fredrickson S Diabetes Care 2004 (6) (nephropathy)	One (43 year male patient)	Pre-post intervention in single subject newly diagnosed with T2D	Intervention: 1,500 calorie ADA diet (with maintained dietary fat composition of 35% but transition to stanols from animal fats) 5-6 days weekly aerobic exercise (running/ elliptical) and upper-body resistance exercise with caloric expenditure 600 kcal/exercise session initially and ultimately 1,000 kcal/exercise session	Microalbuminuria resolved over 24 months (from 70 to 9 mg/gm urinary creatinine) Significant decreases as well in: Fasting sugar (380 to 95 mg/dL over 3 months) Fasting TG (320 to 41 mg/dL over 3 months) HDL cholesterol l (37 to 61 mg/dL over 9 months) LDL cholesterol (210 to 88 mg/dL over 9 months) BP (140/90 to 105/65, normalized within 9 months) BMI (33 to <26 over 3 months, to target 23 by 15 months) Note: no medications added other than 1) glipizide, 5 mg daily * 6 weeks, stopped due to hypoglycemic symptoms at that time and 2) aspirin, 81 mg daily.

Table G3.A14. Summary of Individual Diabetes Exercise/Physical Activity Studies for Treatment of Diabetic Neuropathy, Nephropathy, or Retinopathy That Were Not Both Randomized and Controlled (Note: No Studies Were Both Randomized and Controlled) (continued)

Author, Journal, Year (Type of Microvascular Complication, e.g., Neuropathy, Nephropathy, or Retinopathy)	N	Random/Control	Intervention/Measures	Finding
Colberg SR J Diabetes Complications 2005 (7) (ulcer prevention weight resistance training cutaneous perfusion)	N = 19 (9 sedentary subjects with T2D vs. 10 obese, sedentary non-diabetic controls)	Pre-post analysis	Intervention: 10-week exercise program (3x/week aerobic training at 50-65% HR reserve for 20-45 minutes [duration increased over middle 7 weeks]) Dorsal foot cutaneous perfusion at rest and after thermal vasodilation	After exercise training, both DM subjects and controls had significant ↓ in resting SBP and % body fat (P <0.05) and significant ↑ in VO_{2peak}, but neither group showed improvement in cholesterol (total cholesterol, LDL, HDL) nor in HbA1c. DM group metabolic characteristics were significantly worse than controls at both baseline/post-exercise in HbA1c, fasting glucose, fasting insulin (P <0.05). Resting perfusion similar between groups pre- and post-training Thermal vasodilation perfusion significantly lower in DM vs. control pre-training (107 vs. 69, P <0.05), difference attenuated after training (110 vs. 76, P = NS) Interstitial NO levels comparable between subjects at rest with thermal vasodilation
Colberg SR Microvasc Res 2006 (8) (ulcer prevention weight resistance training cutaneous perfusion)	N =19 (9 sedentary T2D vs. 10 obese, sedentary non-diabetic controls)	Pre-post analysis	Intervention: 8-week supervised resistance training (3 sets 8-12 reps of 50, 60, 70% subject's maximum weight on each of 8 machines) Dorsal foot cutaneous perfusion at rest and after thermal vasodilation	Training led to increased maximum weight lifted x 1 rep in each group, and change in VO_{2peak} in DM group. DM group with significantly lower VO_{2peak} and A1c both at study entry and exit. No difference between DM and control groups in perfusion at rest or with thermal vasodilation. Statistically insignificant decreases in perfusion at rest and increase in perfusion with thermal vasodilation in both DM and control groups.
Smith AG Diabetes Care 2006 (9) (neuropathy)	40 (20 men, 20 women)	Pre-Post intervention in IGT subjects with neuropathy 2º to IGT No control group	DPP-modeled lifestyle intervention: target 7% weight loss and 150 minutes exercise/week Skin biopsy for quantitative nerve fiber density (IENFD) Neuropathic pain scales Electrophysiologic tests (e.g., NCV nerve conduction study)	↓ neuropathy in proximal thigh (P <0.004) and trend towards benefit in distal leg (P <0.12) by IENFD on skin biopsy Trend towards ↓ neuropathic pain on Gracely scale (P <0.1) and non-significant improvement on visual analog pain scale (P <0.4) No significant change in nerve conduction study, but significant correlations between some changes in electrophysiologic measures and improved IENFD suggest possible Type II error

Table G3.A14. Summary of Individual Diabetes Exercise/Physical Activity Studies for Treatment of Diabetic Neuropathy, Nephropathy, or Retinopathy That Were Not Both Randomized and Controlled (Note: No Studies Were Both Randomized and Controlled) (continued)

Author, Journal, Year (Type of Microvascular Complication, e.g., Neuropathy, Nephropathy, or Retinopathy)	N	Random/Control	Intervention/Measures	Finding
Lazarevic G Ren Fail 2007 (10) (nephropathy)	60 men (30 T2D – 6 with microalbuminuria at baseline: 30 non-diabetic)	Pre-post analysis weight resistance training exercise intervention Not randomized +Control	Intervention: Exercise 3-5 x/week for 45-60 minutes at 50-70% maxHR x 6 months Measures: 1: Urinary albumin excretion	Decrease in number of patients with microalbuminuria from 6 (20% sample) at baseline to 3 (10%) at 3 months to 1 (3.3%) at 6 months Non-significant 45% reduction in urinary albumin excretion signals possible benefit (under-powered)

↓, decrease; ADA, American Diabetes Association; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; DPP, Diabetes Prevention Program; FF, filtration fraction; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; IBW, ideal body weight; IENFD, intraepidermal nerve fiber density; IGT, impaired glucose tolerance; IRP, ischemic reperfusion; LDL, low-density lipoprotein; N, numbers; NO, nitric oxide; OGTT, oral glucose tolerance test; RPF, renal plasma flow; SBP, systolic blood pressure; T1D, type 1 diabetes; T2D, type 2 diabetes; TG, triglycerides; U-B2MG, urinary B2 microglobulin

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