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Physical Activity, Muscle-Strengthening Activities, and Systemic Inflammation Among Retinopathy Patients

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ABSTRACT

Objective. We evaluated the specific association between muscle-strengthening activity (MSA) and accelerometer-assessed physical activity on systemic inflammation among retinopathy patients in the United States.

Methods. Data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) were used to identify 157 retinopathy patients between 40 and 85 years of age with complete data on select study variables. MSA was assessed via self-report. Participation in moderate-to-vigorous physical activity (MVPA) was determined from objective accelerometer data. Systemic inflammation was assessed using C-reactive protein (CRP), which was quantified using latex-enhanced nephelometry. Nonproliferative retinopathy was determined using Early Treatment Diabetic Retinopathy Study grading criteria, as well as objective retinal imaging assessments using the Canon Non-Mydriatic Retinal Camera CR6-45NM. Individuals were excluded if they had been diagnosed with coronary artery disease, congestive heart failure, heart attack, or stroke.

Results. MVPA (β = –0.004, 95% CI –0.007 to –0.001, P = 0.006) but not MSA (β = –0.0001, 95% CI –0.002 to 0.001, P = 0.86) was associated with lower CRP levels. Additionally, for a more substantive 30 minutes/day increase in MVPA, there was a corresponding 0.12 mg/dL decrease in CRP.

Conclusion. In this nationally representative sample of adults, only individuals who engaged in higher levels of MVPA had lower CRP levels, which is indicative of reduced systemic inflammation. MSA was not associated with systemic inflammation among this cohort. Our findings suggest that MVPA is inversely associated with systemic inflammation among retinopathy patients, which is noteworthy because increased systemic inflammation may facilitate retinopathic severity.

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Retinopathy is a microvascular pathology of the neural tissue of the retina (1). A cascade of neural degradation often precedes vascular lesions, evolving in line with a litany of widespread health complications identifiable in poorly managed diabetes (1). Microvascular constriction determines the severity of retinal blood flow impediment and promotes the proliferation of new blood vessels (2). However, such abnormal angiogenesis may progressively occlude vision among patients with retinopathy. Perfusion imbalances also initiate widespread vascular constriction, which further contributes to retinal ischemia (3). Specifically, vascular endothelial growth factor, in addition to a multitude of growth factor hormones and proinflammatory cytokines, has been associated with hyperglycemia, insulin resistance, and retinopathy (4–7). High blood pressure has been implicated in vascular endothelial growth factor release,

vessel derangement, and increase in mitochondrial free radicals and ischemia (8,9). Mitochondrial function is at pronounced risk under conditions of hyperglycemia. If retinal mitochondria are damaged, optimal cellular activity may be halted indefinitely; thus, DNA will also be irreversibly destroyed (10). It is well established that retinopathy is exacerbated by several pathological biochemical interactions, wherein critically insidious characteristics of retinopathic development may be illuminated by biomarkers of proinflammation (11).

C-reactive protein (CRP) has been shown to be associated with retinopathy (12). CRP has been used as a plasma measure of inflammation, with evidence suggesting it may be a predictive marker of retinopathy among both diabetic and nondiabetic populations (13–15) although, notably, inflammation is higher among patients diagnosed with type 1 or type 2 diabetes (13,14). Alterations in retinal structure and function may present in individuals without a preexisting diagnosis of retinopathy. Risks common to retinal dysfunction include hypertension, abnormal lipid profile, and obesity (16). Physical activity and muscle-strengthening activity (MSA) are plausibly capable of improving inflammatory responses linked to retinopathy in both healthy and diseased populations. MSA may reduce fat mass and improve body composition (17), thus providing plausibility for strength training to improve the lipid profile and help with successful weight management and, ultimately, inflammatory regulation. In addition, past work shows that aerobic-based physical activity substantially increases lipolysis (18) and reduces systemic inflammation (19). Although distinct in mechanism of action and modality, physical activities involving both aerobic-based and MSA components may exert complementary health benefits on retinopathic prognosis and disease severity (20–26). However, we are unware of any study that has specifically evaluated the independent associations of aerobic-based physical activity and MSA on systemic inflammation among adults with evidence of retinopathy. Therefore, the specific aim of this study was to evaluate the potential association of total physical activity and MSA on CRP, an established biomarker of inflammation and retinopathy progression, among a sample of retinopathy patients.

Methods

Design

Data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) was used. Study procedures were approved by the National Center for Health Statistics ethics review board, with informed consent obtained before data collection.

The NHANES is an ongoing survey conducted by the Centers for Disease Control and Prevention that uses a representative sample of noninstitutionalized U.S. civilians selected by a complex, multistage, stratified, clustered probability design. The design consists of four stages, including the identification of counties, segments (city blocks), random selection of households within the segments, and random selection of individuals within the households. Further information on NHANES methodology and data collection is available on the NHANES website (www.cdc.gov/nchs/nhanes.htm).

Participants

The analyzed sample included 157 participants with complete data on the study variables who had evidence of mild or moderate-to-severe nonproliferative retinopathy and who did not have a physician's diagnosis of coronary artery disease, congestive heart failure, heart attack, or stroke; participants were excluded if they had these conditions because these parameters may have confounded our investigated association between physical activity and systemic inflammation among those with retinopathy. The participants ranged in age from 40 to 85 years.

Retinopathy

As we have described elsewhere (27,28), retinal imaging was performed using the Canon Non-Mydriatic Retinal Camera CR6-45NM (Canon, Tokyo, Japan). The presence of nonproliferative retinopathy (mild or moderate/severe retinopathy) was determined using the Early Treatment Diabetic Retinopathy Study grading criteria (29).

Systemic Inflammation

From a blood sample, CRP was assessed as a marker of systemic inflammation. High-sensitivity CRP concentration was quantified using latex-enhanced nephelometry.

Measurement of Physical Activity

Physical activity was assessed for up to 7 days using an ActiGraph 7164 accelerometer; activity counts/minute ≥2,020 defined participation in moderate-to-vigorous physical activity (MVPA) (30), with individuals having at least 4 days of ≥10 hours/day of monitoring included in the analyses. Non–wear-time was identified as ≥60 consecutive minutes of zero activity counts, with allowance for 1–2 minutes of activity counts between 0 and 100. Specific details regarding the NHANES accelerometer protocol have been previously published (31).

Measurement of MSA

Participants were asked one to two questions related to engagement in MSA: *1*) "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles such as lifting weights, pushups, or sit-ups?" (response option: "yes" or "no") and *2*) individuals answering "yes" to the first question were then asked, "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles such as lifting weights, pushups, or sit-ups?" These exact NHANES MSA items have provided evidence of convergent validity (e.g.,

were shown to be associated with cardiovascular-related parameters [32] and insulin sensitivity [33]). Further, we calculated knee extremity strength (using a Kin Com MP dynamometer) among individuals reporting and not reporting engagement in MSA (≥50 years of age); individuals reporting engagement in MSA (unweighted mean: 296.9 N) had greater knee extensor strength than individuals not reporting engagement in MSA (unweighted mean: 266.0 N) (P <0.05), providing some evidence of construct validity for this MSA item. Notably, these estimates were not from the NHANES cycle in the present study (2005–2006) but rather were from the 1999–2002 NHANES cycles because the 1999–2002 cycles are the only ones with lower-extremity strength data.

TABLE 1. Weighted Characteristics of the Study Variables (n = 157)

Variable	Point Estimate (SE)
MVPA, mean minutes/day	21.6 (2.1)
MSA, mean sessions/month	5.1 (2.7)
Age, mean years	56.3 (1.6)
BMI, mean kg/m^2	29.2 (0.4)
CRP, mean mg/dL	0.45 (0.1)
Sex, % female	42.9
Race/ethnicity, %	
Non-Hispanic white	73.3
Current smoker, %	28.1
Diabetes, %	70.1
Hypertension, %	45.1
Vision impairment, %	2.0
Retinopathy status, %	
Mild	87.7
Moderate-to-severe	12.3

Analysis

All statistical analyses, computed in Stata version 12 (StataCorp., College Station, Tex.), accounted for the complex survey design used in NHANES. A weighted multivariable linear regression was used, with the outcome variable being CRP and the main independent variables being accelerometer-assessed MVPA (minutes/day) and MSA (number of sessions/month). This model also included the following covariates: age (years; continuous), sex, race/ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, other), self-reported smoking status (current, former, never-smoker), measured BMI (continuous; kg/m^2), diabetes status (yes/no), physician-diagnosed hypertension (yes/no), objectively measured visual acuity (34) (normal vision, uncorrected refractive effort, and vision impairment), and objectively measured retinopathy status (mild/moderate-to-severe). With regard to diabetes status, participants were defined as having diabetes if they had a physician's diagnosis, had a fasting blood glucose of ≥126 mg/dL, had an A1C ≥6.5%, or were taking any diabetes medications. Significance was set at P <0.05.

Results

Table 1 displays the weighted characteristics of the sample. Participants, on average, were 56 years old; mean MVPA was 21.6 minutes/day; mean MSA was 5.1 sessions/month; mean CRP was 0.45 mg/dL; 70% had diabetes; and 87.7 and 12.3% had mild and moderate-to-severe retinopathy, respectively.

Regarding the main findings, only MVPA and not MSA was independently associated with lower CRP among individuals in the retinopathy sample. In a model that only included MVPA and MSA as independent variables, MVPA (β = –0.007, 95% CI –0.01 to –0.005, P <0.001) but not MSA (β = –0.001, 95% CI –0.003 to 0.0008, P = 0.23) was associated with CRP. In the adjusted model (Table 2), results were similar, in that MVPA (β = –0.004, 95% CI –0.007 to –0.001, P = 0.006) but not MSA (β = –0.0001, 95% CI –0.002 to 0.001, P = 0.86) was associated with lower CRP levels. For example, for a 1 minute/day increase in MVPA, there was a corresponding 0.004 mg/dL decrease in CRP. When expressed as a larger interval change (30 minutes/day), for a 30 minutes/day increase in MVPA, there was a corresponding 0.12 mg/dL decrease in CRP.

A follow-up analysis expressed CRP as a binary variable, categorized as elevated (≥0.3 mg/dL) or not (<0.3 mg/dL). In an adjusted logis-

TABLE 2. Adjusted Regression Results Examining the Association Between Physical Activity and Muscle-Strengthening Activities on CRP

	Linear Regression			Logistic Regression		
	β	95% CI	P	OR	95% CI	P
MVPA, minutes/day	–0.004	–0.007 to –0.001	0.006	0.93	0.89–0.96	0.001
MSA, sessions/month	0.0001	–0.002 to 0.001	0.86	0.94	0.83–1.07	0.33

tic regression model, for a 1 minute/day increase in MVPA, retinopathy patients had a 7% reduced odds of having an elevated CRP (odds ratio [OR] 0.93, 95% CI 0.89–0.96, $P = 0.001$). When expressed as a larger interval change, for a 30 minutes/day increase in MVPA, there was a corresponding 88% reduced odds of having an elevated CRP (OR 0.12, 95% CI 0.04–0.39; $P = 0.001$).

Discussion

Previous research highlights the attenuating benefit of physical activity on inflammatory mechanisms in healthy and diseased populations (17,19,25,26). Therefore, the purpose of our study was to extend this literature by examining the association of MSA and accelerometer-assessed physical activity on CRP among individuals with retinopathy because elevated systemic inflammation has been shown to facilitate the progression of retinopathy disease (14–16,35). Our main finding was that, among individuals engaging in higher levels of MVPA, CRP levels were reduced, whereas participation in MSA did not have a statistically significant influence on CRP.

Our findings demonstrate that even modest increases in physical activity may have a positive impact on retinopathic outcomes. For every additional 30-minute increase in MVPA, there was an associated 0.12 mg/dL decrease in CRP and an 88% reduced odds of having an elevated CRP. β-Adrenergic receptors are suggested to stimulate fat cells and increase pro-inflammation by way of cytokine mobilization (36,37). Physical activity may alter β-adrenergic receptor density and expression, curtailing their stimulatory effect on adipose tissue (38). Another possible mechanism by which this interaction may develop is the association between physical activity and stress reduction. High levels of stress may accelerate depression and anxiety, and the release of pro-inflammatory cytokines (39–41). A stronger clinical approach should perhaps focus on limiting retinopathy progression with physical activity in combination with individual stress-management strategies.

MSA data were self-reported, which augments the need for increased sample size to maximize potential for statistical significance, as questionnaire-based estimations tend to foreshadow weakened effect size (42). In addition to the risk of erroneous estimations in subjectively reported data, another potential explanation for the negligible influence of MSA on CRP status is the low frequency of resistance-training participation reported by participants in the present sample. On average, participants engaged in only five sessions of MSA per month, which is likely insufficient to favorably mitigate inflammation. The American College of Sports Medicine and the American Heart Association recommend engaging in at least two sessions of MSA per week for optimal health benefits, particularly among aging individuals (43,44). Future work should examine associations between MSA and retinopathy, with participant adherence to appropriate levels of activity closely monitored.

In conclusion, this study identifies the association between accelerometer-assessed MVPA participation and lower plasma measures of CRP among aging individuals with a nonproliferative retinopathy diagnosis. Our findings amplify important conclusions from previous research suggesting the multifactorial impact of physical activity on retinopathic biomarkers. We specifically examined the plausibility for aerobic-based, as well as resistance training, modalities to reduce concentration of plasma CRP among people with existing retinopathy. We identified a relationship between MVPA engagement and CRP reduction. This finding is noteworthy because elevated inflammation may facilitate retinopathy disease progression (14–16,35,45). Our use of a cross-sectional research design, in addition to self-reported MSA, are limitations that should be addressed in future longitudinal investigations.

Author Contributions

E.F. and P.D.L. contributed to writing the manuscript, and P.D.L. computed the analyses. P.D.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Antonetti DA, Barber AJ, Bronson SK, et al. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes 2006;55:2401–2411

2. Durham JT, Herman IM. Microvascular modifications in diabetic retinopathy. Curr Diab Rep 2011;11:253–264

3. Barot M, Gokulgandhi MR, Patel S, Mitra AK. Microvascular complications and diabetic retinopathy: recent advances and future implications. Future Med Chem 2013;5:301–314

4. Abcouwer SF. Angiogenic factors and cytokines in diabetic tetinopathy. J Clin Cell Immunol 2013;Suppl 1:1–12 (DOI: 10.4172/2155-9899)

5. Costagliola C. Oxidative state of glutathione in red blood cells and plasma of diabetic patients: in vivo and in vitro study. Clin Physiol Biochem 1990;8:204–210

6. Ellis TP, Choudhury RH, Kaul K, et al. Diabetic retinopathy and atherosclerosis: is there a link? Curr Diabetes Rev 2013;9:146–160

7. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. ISRN Ophthalmol 2013;2013:343560

8. Gologorsky D, Thanos A, Vavvas D. Therapeutic interventions against inflammatory and angiogenic mediators in proliferative diabetic retinopathy. Mediators Inflamm 2012;2012:629452

9. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res 2011;30:343–358

10. Sone H, Kawakami Y, Okuda Y, et al. Vascular endothelial growth factor is induced by long-term high glucose concentration and up-regulated by acute glucose deprivation in cultured bovine retinal pigmented epithelial cells. Biochem Biophys Res Commun 1996;221:193–198

11. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, Costagliola C. Diabetic retinopathy: vascular and

inflammatory disease. J Diabetes Res 2015;2015:582060

12. van Hecke MV, Dekker JM, Nijpels G, et al. Inflammation and endothelial dysfunction are associated with retinopathy: the Hoorn Study. Diabetologia 2005;48:1300–1306

13. Kado S, Nagata N. Circulating intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 1999;46:143–148

14. Schalkwijk CG, Poland DC, van Dijk W, et al. Plasma concentration of C-reactive protein is increased in type I diabetic patients without clinical macroangiopathy and correlates with markers of endothelial dysfunction: evidence for chronic inflammation. Diabetologia 1999;42:351–357

15. Jager A, van Hinsberg VW, Kostense PJ, et al. von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects: the Hoorn Study. Arterioscler Thromb Vasc Biol 1999;19:3071–3078

16. van Leiden HA, Dekker JM, Moll AC, et al. Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn Study. Diabetes Care 2002;25:1320–1325

17. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002;25:2335–2341

18. Holloszy JO, Booth FW. Biochemical adaptations to endurance exercise in muscle. Annu Rev Physiol 1976;38:273–291

19. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among US adults. Epidemiology 2002;13:561–568

20. Buckner SL, Loenneke JP, Loprinzi PD. Single and combined associations of accelerometer-assessed physical activity and muscle-strengthening activities on plasma homocysteine in a national sample. Clin Physiol Funct Imaging 2016;37:669–674

21. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA 2010;304:2253–2262

22. Dankel SJ, Loenneke JP, Loprinzi PD. Participation in muscle-strengthening activities as an alternative method for the prevention of multimorbidity. Prev Med 2015;81:54–57

23. Dankel SJ, Loenneke JP, Loprinzi PD. The individual, joint, and additive interaction associations of aerobic-based physical activity and muscle strengthening activities on metabolic syndrome. Int J Behav Med 2016;23:707–713

24. Dankel SJ, Loenneke JP, Loprinzi PD. Determining the importance of meeting muscle-strengthening activity guidelines: is the behavior or the outcome of the behavior (strength) a more important determinant of all-cause mortality? Mayo Clin Proc 2016;91:166–174

25. Dankel SJ, Loenneke JP, Loprinzi PD. Combined associations of muscle-strengthening activities and accelerometer-assessed physical activity on multimorbidity: findings from NHANES. Am J Health Promot 2016;31:274–277

26. Loprinzi PD, Loenneke JP, Abe T. The association between muscle strengthening activities and red blood cell distribution width among a national sample of U.S. adults. Prev Med 2015;73;130–132

27. Loprinzi PD. Association of accelerometer-assessed sedentary behavior with diabetic retinopathy in the United States. JAMA Ophthalmol 2016;134:1197–1198

28. Loprinzi PD, Brodowicz GR, Sengupta S, Solomon SD, Ramulu PY. Accelerometer-assessed physical activity and diabetic retinopathy in the United States. JAMA Ophthalmol 2014;132:1017–1019

29. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98 (5 Suppl):786–806

30. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181

31. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. Br J Sports Med 2014;48:1019–1023

32. Loprinzi PD, Loenneke JP, Abe T. The association between muscle strengthening activities and red blood cell distribution width among a national sample of U.S. adults. Prev Med 2015;73:130–132

33. Cheng YJ, Gregg EW, De Rekeneire N, et al. Muscle-strengthening activity and its association with insulin sensitivity. Diabetes Care 2007;30:2264–2270

34. Loprinzi PD, Pariser G, Ramulu PY. Accelerometer-assessed sedentary and physical activity behavior and its association with vision among U.S. adults with diabetes. J Phys Act Health 2014;11:1156–1161

35. van Leiden HA, Dekker JM, Moll AC, et al. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn Study. Arch Ophthalmol 2003;121:245–251

36. Kohut ML, McCann DA, Russell DW, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav Immun 2006;20:201–209

37. Nieto JL, Laviada ID, Guillen A, Haro A. Adenylyl cyclase system is affected differently by endurance physical training in heart and adipose tissue. Biochem Pharmacol 1996;51:1321–1329

38. Jenkins NP, Keevil BG, Hutchinson IV, Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. Am J Med 2002;112:269–274

39. Black PH. Stress and the inflammatory response: a review of neurogenic inflammation. Brain Behav Immun 2002;16:622–653

40. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. J Psychosom Res 2002;52:1–23

41. Suarez EC. C-reactive protein is associated with psychological risk factors of cardiovascular disease in apparently healthy adults. Psychosom Med 2004;66:684–691

42. Tooze JA, Troiano RP, Carroll RJ, Moshfegh AJ, Freedman LS. A measurement error model for physical activity level as measured by a questionnaire with application to the 1999–2006 NHANES questionnaire. Am J Epidemiol 2013:177:1199–1208

43. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423–1434

44. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1435–1445

45. Rangasamy S, McGuire PG, Das A. Diabetic retinopathy and inflammation: novel therapeutic targets. Middle East Afr J Ophthalmol 2012;19:52