Title

Association Between Metformin Use and Cognitive and Physical Function in Persons with HIV and Diabetes

Journal

AIDS Research and Human Retroviruses, 39(6)

ISSN

0889-2229

Authors

Masters, Mary Clare

Granche, Janeway

Yang, Jingyan

et al.

Publication Date

2023-06-01

DOI

10.1089/aid.2022.0129

Peer reviewed

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 39, Number 6, 2023

DOI: 10.1089/aid.2022.0129

Association Between Metformin Use and Cognitive and Physical Function in Persons with HIV and Diabetes

Mary Clare Masters,[1] Janeway Granche,[2] Jingyan Yang,[3] Edgar T. Overton,[4] Scott Letendre,[5] Susan L. Koletar,[6] Leah H. Rubin,[7] Todd T. Brown,[8] Katherine Tassiopoulos,[2] Kristine M. Erlandson,[9] and Frank Palella[1]

Abstract

Older persons with HIV (PWH) experience high rates of cognitive impairment and frailty, and accelerated decline in physical function compared with the general population. Metformin use has been associated with beneficial effects on cognitive and physical function among older adults without HIV. The relationship between metformin use on these outcomes in PWH has not been evaluated. AIDS Clinical Trials Group (ACTG) A5322 is an observational cohort study of older PWH with annual assessments for cognition and frailty, including measures of physical function (e.g., gait speed and grip strength). Participants with diabetes who were prescribed antihyperglycemic medications were included in this analysis to evaluate the association between metformin and functional outcomes. Cross-sectional, longitudinal, and time-to-event models were used to evaluate the relationship between metformin exposure with cognitive, physical function, and frailty outcomes. Ninety-eight PWH met inclusion criteria and were included in at least one model. No significant associations between metformin use, frailty, physical, or cognitive function were noted in unadjusted or adjusted cross-sectional, longitudinal, or time-to-event models ($p > .1$ for all models). This study is the first to examine the association between metformin use on functional outcomes among older PWH. Although it did not ascertain significant associations between metformin use and functional outcomes, our small sample size, restriction to persons with diabetes, and lack of randomization to metformin therapy were limitations. Larger randomized studies are needed to determine whether metformin use has beneficial effects on cognitive or physical function in PWH. Clinical Trial Registration numbers: 02570672, 04221750, 00620191, and 03733132.

Keywords: metformin, HIV, frailty, physical function, aging

Introduction

Routine use of virally suppressive antiretroviral therapy (ART) markedly extends the lifespan of persons with HIV (PWH), which now approaches that of the general population. Effective ART has not, however, had a similar effect on the health span of PWH, who experience both earlier onset and increased rates of noninfectious, aging-related comorbidities compared with the general population.[1,2] Older PWH have higher rates of cognitive impairment and frailty than people without HIV, as well as accelerated declines in physical function.[3–6] These aging-related

[1]Department of Internal Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.
[2]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.
[3]Institute for Social and Economic Research and Policy, Columbia University, New York, New York, USA.
[4]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[5]Department of Medicine, University of California, San Diego, La Jolla, California, USA.
[6]Department of Internal Medicine, Ohio State University, Columbus, Ohio, USA.
[7]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA.
[8]Department of Medicine, Johns Hopkins University, Maryland, USA.
[9]Department of Medicine, University of Colorado, Aurora, Colorado, USA.

syndromes are associated with adverse health outcomes in PWH, including disability, reduced quality-of-life, and mortality.[7–11] Interventions to alleviate such physical and cognitive impairment are currently limited for PWH.

Increasing evidence suggests that metformin, a first-line medication for the treatment of type 2 diabetes mellitus (DM), may be beneficial for the treatment of impaired cognitive and physical function in aging people without HIV. In addition to improving insulin sensitivity and counteracting hyperglycemia, metformin also targets key aging mechanisms, including inflammation[12,13] and cellular senescence.[14,15] Prior reports have indicated that metformin can improve gait speed[16] and is associated with lower risk of frailty in diabetic older adults.[17,18] Several studies have also shown that metformin use is associated with preservation of cognitive function.[19–22] Among older adults without HIV, ongoing clinical trials are investigating the impact of metformin on cognitive, mobility, and frailty outcomes (ClinicalTrials.gov Identifier).

Abnormal glucose metabolism[23,24] and chronic inflammation[25,26] are associated with premature onset of frailty and impaired cognitive and physical function in PWH. Thus, metformin may have particular benefit in preventing or alleviating functional impairment in PWH. Since the relationship between metformin exposure and cognitive and physical function in PWH have not yet been evaluated, this study aimed to address this gap by analyzing data from PWH with diabetes in the AIDS Clinical Trials Group (ACTG) study A5322, which is also known as HAILO (HIV Infection, Aging, and Immune Function Long-term Observational Study).

Methods

Study population

This study used existing data from HAILO, an observational multisite cohort study of older PWH. All HAILO participants initiated ART through an ACTG randomized clinical trial and were subsequently followed in ACTG A5001, the predecessor of HAILO.[27] Between November 2013 and July 2014, a subset of A5001 participants ($n = 1{,}035$) ≥40 years old were enrolled in HAILO for continued observational follow-up. This analysis includes data from HAILO entry though week 288.

Participants with diabetes who were receiving antihyperglycemic medications and who had at least one outcome measure of interest were considered for inclusion. Diabetes diagnosis was defined as meeting at least one of the following criteria: (1) prior diagnosis of type 2 diabetes; (2) two laboratory assessments at the same or consecutive visits in the diabetic range [hemoglobin A1C (HbA1c) ≥6.5% or fasting blood sugar ≥126 mg/dL]; or (3) prescription of an antihyperglycemic medication (including insulin) with at least one laboratory assessment in the diabetic range within a year of starting medication. Included participants were classified as metformin users or nonusers. Metformin use was defined as use of metformin for at least 365 days with no treatment gaps for at least 60 days. Participants were excluded if they had a history of renal disease, which was defined as more than one estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at least 3 months apart with no intervening eGFR ≥60 using the CKD-EPI equation.

Outcomes

Cognitive performance was evaluated annually using the A5001 Neuroscreen, which includes the Trail Making A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol test.[4] Cognitive performance is summarized in a demographically adjusted mean z-score, the NPZ3.[28] Cognitive impairment was defined as at least one z-score ≥2 standard deviations (SDs) below the mean or at least two z-scores ≥1 SD below the mean on separate tests within the A5001 Neuroscreen. Frailty was assessed annually using the Fried Frailty Phenotype components of grip strength, 4-m walk speed, and self-reported low activity, exhaustion, and unintentional weight loss.

Individuals meeting 3–5 criteria were considered frail; 1–2, prefrail; and 0, robust. For models involving categorical frailty, participants were categorized either as frail or nonfrail (prefrail/robust).[29] Gait speed (walk time) was defined as the mean time in seconds of two 4-m walks. For categorical models, assessments with a mean time >4 s were defined as ''slow'' (vs. not slow). Grip strength was measured in kilograms as the mean of three grip tests. Grip strength was coded as ''weak'' (vs. not weak) depending on participant sex and body mass index (BMI).[30]

Covariates

Covariates included sex at birth (male/female), age, race/ethnicity, HbA1c (%), BMI (kg/m^2), duration of diabetes (years), suppressed HIV-1 RNA (<50 copies/mL), and smoking status (classified as never, former, or current). Cross-sectional models were adjusted for baseline BMI, duration of diabetes, and HbA1c. Longitudinal and time-to-event models were adjusted for baseline BMI, duration of diabetes and time-updated HbA1c.

Statistical analysis

Cross-sectional, longitudinal, and time-to-event models analyzed the relationship between metformin exposure and cognitive, physical function, and frailty outcomes among HAILO participants with diabetes who were prescribed antihyperglycemic medications. The definitions for baseline and the duration of follow-up differed by analysis type and are described for each model as follows. Baseline characteristics by metformin use were evaluated in each model. Fisher's exact tests were used for categorical variables and the two-sample Wilcoxon test with continuity correction for continuous variables.

Cross-sectional associations between metformin use with frailty, weak grip, slow gait, and cognition were estimated using robust Poisson models. The first assessment of the outcome in question was the data point used for these models.

Longitudinal analyses used mixed models with fixed effects and random intercepts to estimate differences in trajectories in NPZ3 score, grip strength, and walk time by metformin use. For these models, baseline was defined as the latest of (1) first outcome assessment, (2) diabetes diagnosis, or (3) start of metformin use when applicable. For participants who stopped metformin use during follow-up, only the observations occurring during metformin use were included. Models were estimated using the residual (restricted) maximum likelihood method. Random intercepts and slopes were

Table 1. Baseline Characteristics for Frailty Model

	Cross-sectional			*Longitudinal*			*Time-to-event*		
	On metformin (n = 59)	*Not on metformin (n = 10)*	p	*On metformin (n = 70)*	*Not on metformin (n = 17)*	p	*On metformin (n = 59)*	*Not on metformin (n = 15)*	p
Age (years)	55.2 (49.5, 61.3)	56.3 (46.0, 63.2)	.79	54.3 (49.5, 60.8)	55.9 (48.8, 62.7)	.85	55.2 (49.1, 60.9)	56.6 (46.0, 63.2)	.72
Female sex at birth	15 (25%)	0 (0%)	.10	20 (29%)	4 (24%)	.77	14 (24%)	3 (20%)	1.00
Race/ethnicity			.11			.33			.48
White non-Hispanic	19 (32%)	1 (10%)		25 (36%)	7 (41%)		22 (37%)	6 (40%)	
Black non-Hispanic	19 (32%)	7 (70%)		20 (29%)	7 (41%)		16 (27%)	6 (40%)	
Hispanic	21 (36%)	2 (20%)		25 (36%)	3 (18%)		21 (36%)	3 (20%)	
BMI (kg/m^2)	29.4 (26.2, 35.2)	28.8 (26.2, 29.8)	.29	29.7 (26.5, 35.2)	28.6 (25.2, 30.6)	.05	29.9 (26.3, 35.1)	28.6 (23.3, 30.6)	.05
HbA1c (%)	7.2 (6.2, 8.5)	7.5 (6.0, 11.3)	.73	7.2 (6.3, 8.1)	7.1 (6.0, 8.1)	.56	7.2 (6.4, 8.1)	6.8 (5.9, 8.1)	.32
Duration of diabetes (years)	6.2 (4.0, 10.1)	8.1 (5.2, 12.0)	.32	4.9 (1.7, 8.5)	7.6 (0.8, 11.3)	.74	4.9 (1.5, 8.5)	7.6 (0.8, 11.3)	.66
Smoking status			.35			.10			.42
Never	25 (43%)	5 (50%)		31 (44%)	6 (35%)		26 (44%)	6 (40%)	
Former	24 (41%)	2 (20%)		27 (39%)	4 (24%)		23 (39%)	4 (27%)	
Current	9 (16%)	3 (30%)		12 (17%)	7 (41%)		10 (17%)	5 (33%)	
HIV RNA <50 copies/mL	54 (92%)	8 (80%)	.27	67 (96%)	15 (88%)	.25	56 (95%)	14 (93%)	1.00
Slow gait	35 (59%)	6 (60%)	1.00	44 (63%)	10 (59%)	.79	35 (59%)	8 (53%)	.77
Weak grip	28 (47%)	4 (40%)	.74	30 (43%)	8 (47%)	.79	21 (36%)	6 (40%)	.77
Frail	11 (19%)	2 (20%)	1.00	11 (16%)	2 (12%)	1.00	—	—	—

Median (Q1, Q3) or count (%); continuous variables tested with Wilcoxon test; categorical variables tested with Fisher's exact test.
BMI, body mass index; HbA1c, hemoglobin A1C.

Table 2. Baseline Characteristics for Cognitive Impairment Models

	Cross-sectional			*Longitudinal*			*Time-to-event*		
	On metformin (n=60)	*Not on metformin (n=10)*	p	*On metformin (n=62)*	*Not on metformin (n=17)*	p	*On metformin (n=39)*	*Not on metformin (n=13)*	p
Age (years)	55.5 (49.6, 61.6)	56.2 (46.0, 63.8)	.78	54.8 (49.1, 60.4)	55.8 (48.8, 62.7)	.67	55.2 (48.3, 60.4)	54.2 (46.0, 57.8)	.63
Female sex at birth	15 (25%)	0 (0%)	.11	18 (29%)	4 (24%)	.77	5 (13%)	3 (23%)	.40
Race/ethnicity			.13			.51			.77
White non-Hispanic	19 (32%)	1 (10%)		24 (39%)	7 (41%)		16 (41%)	7 (54%)	
Black non-Hispanic	20 (33%)	7 (70%)		19 (31%)	7 (41%)		15 (38%)	4 (31%)	
Hispanic	21 (35%)	2 (20%)		19 (31%)	3 (18%)		8 (21%)	2 (15%)	
BMI (kg/m^2)	29.4 (26.2, 35.1)	29.3 (26.2, 29.7)	.34	29.5 (26.5, 35.1)	28.9 (25.2, 30.6)	.07	29.4 (26.8, 35.2)	28.6 (25.2, 31.2)	.12
HbA1c (%)	7.2 (6.3, 8.1)	7.5 (6.5, 11.3)	.40	7.1 (6.3, 8.1)	7.1 (6.5, 7.4)	.93	7.1 (6.1, 8.5)	7.1 (5.9, 7.4)	.63
Duration of diabetes (years)	6.3 (4.0, 9.8)	8.1 (5.7, 12.0)	.25	5.2 (2.5, 8.9)	7.9 (0.8, 11.4)	.74	5.2 (2.7, 9.2)	5.2 (0.5, 11.3)	.46
Smoking status			.36			.16			.12
Never	24 (41%)	5 (50%)		29 (47%)	6 (35%)		18 (46%)	4 (31%)	
Former	25 (42%)	2 (20%)		22 (35%)	4 (24%)		15 (38%)	3 (23%)	
Current	10 (17%)	3 (30%)		11 (18%)	7 (41%)		6 (15%)	6 (46%)	
HIV RNA <50 copies/mL	57 (95%)	8 (80%)	.15	59 (95%)	15 (88%)	.29	38 (97%)	11 (85%)	.15
Cognitive impairment	18 (30%)	1 (10%)	.27	18 (29%)	2 (12%)	.21	—	—	—

Median (Q1, Q3) or count (%); continuous variables tested with Wilcoxon Test; categorical variables tested with Fisher's exact test.

Table 3. Cross-Sectional Association Between Metformin and Physical and Cognitive Function

		Unadjusted		*Adjusted*[a]	
Model	N	*Risk ratio (95% CI)*	p	*Risk ratio (95% CI)*	p
Metformin use and frailty	69	0.93 (0.24 to 3.59)	.92	1.31 (0.43 to 3.95)	.64
Metformin use and weak grip	69	1.19 (0.53 to 2.65)	.68	1.20 (0.54 to 2.70)	.65
Metformin use and slow gait	69	0.99 (0.57 to 1.71)	.97	1.00 (0.57 to 1.77)	1.00
Metformin use and NC impairment	70	3.00 (0.45 to 20.04)	.26	2.83 (0.37 to 21.71)	.32

[a]Adjusted for BMI, HbA1c, and duration of diabetes.
CI, confidence interval.

tested for inclusion using the likelihood ratio test to compare the differences in the -2RLL (-2 residual log likelihood) scores, and by checking the significance of the covariance parameter estimates. Time was modeled as years (continuous) since baseline. Differences in trajectories were assessed through time × metformin use interaction terms.

Time-to-event models were used to examine the differential hazard of cognitive impairment and frailty by metformin use. Separate interval-censored semiparametric proportional hazards models were evaluated for cognitive impairment and frailty. The time-to-event models used the same definition of baseline as the longitudinal models. However, participants who had experienced the event of interest at or up to 2 years before baseline were excluded. Metformin users who stopped using metformin before experiencing the outcome of interest were censored when they stopped using metformin. Participants who did not experience the outcome of interest during follow-up were censored at their last observation. Proportional hazards assumptions were tested using Martingale residuals.

Results

Of the 1,035 HAILO participants, 98 people with diabetes met all inclusion criteria and were included in at least one model. Of those participants included in the analysis, the baseline median age was 56 years [(Q1–Q3) 50–61]. Seventy-three percent were male sex at birth (gender identity was not collected at study baseline), 33% Black, and 30% Hispanic (of any race). Most individuals had well-controlled HIV infection at study entry: 93% had undetectable plasma HIV-1 RNA with median $CD4^+$ T cells of 642 cells/μL [(Q1–Q3) 389–902]. The median duration of ART was 10 years [(Q1–Q3) 7–17]. The median nadir $CD4^+$ T cell was 171 cells/μL [(Q1–Q3) 24–302]. Participants contributed up to six neurocognitive assessments [median (Q1–Q3): 4 (3–5)] and up to seven frailty assessments [median (Q1–Q3): 4 (3–6)] to the longitudinal models. At study entry, 19% participants were frail, 59% had slow gait, 46% had weak grip, and 27% had NCI.

Baseline characteristics are presented in Table 1 (frailty data) and Table 2 (cognitive data) with no significant differences between groups. Overall, no associations between metformin use and frailty, physical or cognitive performance were noted in unadjusted or adjusted cross-sectional, longitudinal, or time-to-event models (Tables 3 and 4). In cross-sectional models (Table 3), metformin use versus nonuse was not associated with frailty, slow gait, weak grip, or cognitive impairment ($p > .1$ for all models). In longitudinal models (Table 4), the point estimates for metformin use versus nonuse were not significantly associated with grip strength, gait speed, or NPZ3 score ($p > .1$ for all models).

For time-to-event models (Supplementary Tables S1 and S2), few frailty ($n = 9$) or cognitive impairment ($n = 7$) events occurred in follow-up. The adjusted hazard ratio (HR) of frailty was 0.41 (95% confidence interval: 0.07–2.53; $p = .34$). Since no cognitive impairment events occurred among metformin nonusers, a HR could not be estimated. Instead, a log-rank test found no significant difference in time-to-event between the groups ($p = .17$).

Discussion

In this study, we present the first pilot data to evaluate the relationship between metformin use and cognitive function, physical function, and frailty in a well-characterized longitudinally followed cohort of PWH with diabetes. Although we failed to identify a significant relationship between metformin and the functional outcomes, the cohort sample size was small. Larger studies, preferably designed specifically to assess the relationship, are needed to evaluate the effect of metformin on functional outcomes in PWH.

Previous studies have shown that metformin has beneficial effects on cognitive and physical performance in adults

Table 4. Longitudinal Mixed Models: Effect of Metformin on Physical and Cognitive Performance Over Time (Years)

		Unadjusted models		*Adjusted*[a] *models*	
Outcomes	N	*Estimate (95% CI)*	p	*Estimate (95% CI)*	p
Grip strength (kg)	87	–0.36 (–1.27 to 0.54)	.43	–0.38 (–1.29 to 0.52)	.40
Walk time (s)	87	–0.03 (–0.16 to 0.10)	.64	–0.03 (–0.16 to 0.10)	.67
NPZ3 score[b]	79	0.02 (–0.07 to 0.12)	.65	0.02 (–0.07 to 0.12)	.68

[a]Adjusted for baseline BMI, duration of diabetes, and time-updated HbA1C.
[b]Higher NPZ3 score indicates better performance.

without HIV.[19–21] The hypothesis that metformin may improve functional outcomes among PWH is scientifically justified. Metformin can improve cognitive and physical function both through and independent of its effect on glucose metabolism. Abnormal glucose metabolism is associated with impaired cognitive and physical function in both the general population and among PWH.[23,31–37] PWH experience increased incidence and prevalence of diabetes.[38,39] Use of metformin can reduce blood glucose and improve insulin sensitivity, and thereby prevent sequelae of uncontrolled diabetes that contribute to functional impairment in PWH.

Metformin also targets key aging pathways, including inflammation[12,13] and oxidative stress, through mechanistic target of rapamycin (mTOR) inhibition[40] and AMP-activated protein kinase activation.[41,42] Chronic inflammation and immune activation are also linked to increases in frailty and cognitive and physical function impairment among PWH.[25,43] In a small randomized study ($N=22$) evaluating the HIV reservoir in PWH, metformin reduced mTOR activation/phosphorylation as well as colonic $CD4^+$ T cell infiltration.[44] Thus, metformin may have particular benefit in treating or preventing functional impairment in PWH.

Although metformin is widely prescribed for type 2 DM and considered to have a favorable safety profile, potential adverse effects of metformin on functional outcomes must also be acknowledged. Metformin use has been associated with vitamin B12 deficiency,[45] which has been implicated some adverse cognitive outcomes in individuals on long-term therapy.[46] Previous studies have reported that metformin antagonizes the beneficial effects on exercise on insulin sensitivity and muscle quality.[47,48] However, additional analysis has suggested that optimally timing of metformin therapy in conjunction with exercise intervention may have beneficial effects on aging-associated pathways in muscle.[49] Careful evaluation of the risks and benefits of metformin on physical and cognitive function in both older adults with and without HIV is needed.

Significant limitations of this analysis must be acknowledged. The small sample size, particularly of participants with diabetes receiving nonmetformin antihyperglycemics, reduced the power of this analysis. The small sample size also limited the number of covariates that could be included in the models and our ability to assess for interactions between covariates, including between metformin and HIV medications. Although models were controlled for HbA1c and duration of diabetes, it is possible that these adjustments did not fully account for the effects of diabetes severity on cognitive performance and physical function in this study.

Metformin is the first-line treatment for type 2 diabetes; therefore, there may be selection bias among those participants who were treated with only nonmetformin antihyperglycemic agents in this observational cohort study. Furthermore, metformin was prescribed at the discretion of HIV care providers, and we cannot account for any inherent bias that may have introduced. In addition, this study only included PWH who also have diabetes. Our findings do not preclude the possibility that metformin may have benefits on functional outcomes for PWH who do not have diabetes. Larger randomized studies are needed to delineate the effect of metformin on cognitive and physical function outcomes among PWH.

As the population of older PWH grows, the prevalence of frailty, cognitive impairment, and impaired physical function will continue to increase. Interventions to treat or prevent these age-related outcomes in PWH remain limited. In the general aging population, a large clinical trial ($n=3,000$), Targeting Aging with Metformin (TAME), is in development to assess the impact of metformin on aging in the general population.[50] Another ongoing National Institute on Aging-sponsored clinical trial is investigating metformin use to prevent frailty in older adults with prediabetes (Clinical Trials.gov). However, PWH have been excluded from participation in these studies. The results from this limited study highlights the importance of future, more robust investigation of the effect of metformin therapy on cognitive and physical function in PWH. Such studies are needed to advance care for older PWH beyond longevity and toward healthy aging.

Acknowledgments

The authors thank the ACTG A5322 HAILO study participants and clinical research sites.

Ethics Approval and Consent to Participate

All participants signed a written informed consent before enrollment, and the study was approved by the local institutional review board at each site.

Availability of Data and Materials

To protect participants' health information, the data sets generated and/or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Contributions

J.G. performed the analysis under the supervision of K.T. M.C.M. prepared the first draft of the article. All authors contributed to the study design, implementation, interpretation of data, and read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This study was supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health under Award Numbers UM1 AI068634, UM1 AI068636, UM1 AI106701, and UM1 AI069494; National Institute on Aging 5R03AG067980 (PI: M.C.M.) and P30AG059988. T.T.B. is supported in part by K24 AI120834.

Supplementary Material

Supplementary Table S1
Supplementary Table S2

References

1. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011;62:141–155; doi: 10.1146/annurev-med-042909-093756
2. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: The Swiss HIV cohort study. Clin Infect Dis 2011;53(11):1130–1139; doi: 10.1093/cid/cir626
3. Desquilbet L, Jacobson LP, Fried LP, et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci 2007; 62(11):1279–1286.
4. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 2007;21(14):1915–1921; doi: 10.1097/QAD.0b013e32828e4e27
5. Schrack JA, Althoff KN, Jacobson LP, et al. Accelerated longitudinal gait speed decline in HIV-infected older men. J Acquir Immune Defic Syndr 2015;70(4):370–376; doi: 10.1097/QAI.0000000000000731
6. Schrack JA, Jacobson LP, Althoff KN, et al. Effect of HIV-infection and cumulative viral load on age-related decline in grip strength. AIDS 2016;30(17):2645–2652; doi: 10.1097/QAD.0000000000001245
7. Johs NA, Wu K, Tassiopoulos K, et al. Disability among middle-aged and older persons with human immunodeficiency virus infection. Clin Infect Dis 2017;65(1):83–91; doi: 10.1093/cid/cix253
8. Sharma A, Hoover DR, Shi Q, et al. Longitudinal study of falls among HIV-infected and uninfected women: The role of cognition. Antivir Ther 2018;23(2):179–190; doi: 10.3851/IMP3195
9. Tassiopoulos K, Abdo M, Wu K, et al. Frailty is strongly associated with increased risk of recurrent falls among older HIV-infected adults. AIDS 2017;31(16):2287–2294; doi: 10.1097/QAD.0000000000001613
10. Erlandson KM, Allshouse AA, Jankowski CM, et al. Relationship of physical function and quality of life among persons aging with HIV infection. AIDS 2014;28(13): 1939–1943; doi: 10.1097/QAD.0000000000000384
11. Erlandson KM, Perez J, Abdo M, et al. Frailty, neurocognitive impairment, or both in predicting poor health outcomes among adults living with human immunodeficiency virus. Clin Infect Dis 2019;68(1):131–138; doi: 10.1093/cid/ciy430
12. Saisho Y. Metformin and inflammation: Its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets 2015;15(3):196–205.
13. Horiuchi T, Sakata N, Narumi Y, et al. Metformin directly binds the alarmin HMGB1 and inhibits its proinflammatory activity. J Biol Chem 2017;292(20):8436–8446; doi: 10.1074/jbc.M116.769380
14. Fang J, Yang J, Wu X, et al. Metformin alleviates human cellular aging by upregulating the endoplasmic reticulum glutathione peroxidase 7. Aging Cell 2018;17:e12765; doi: 10.1111/acel.12765
15. Moiseeva O, Deschenes-Simard X, St-Germain E, et al. Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kappaB activation. Aging Cell 2013;12(3):489–498; doi: 10.1111/acel.12075
16. Laksmi PW, Setiati S, Tamin TZ, et al. Effect of metformin on handgrip strength, gait speed, myostatin serum level, and health-related quality of life: A double blind randomized controlled trial among non-diabetic pre-frail elderly patients. Acta Med Indones 2017;49(2):118–127.
17. Sumantri S, Setiati S, Purnamasari D, et al. Relationship between metformin and frailty syndrome in elderly people with type 2 diabetes. Acta Med Indones 2014;46(3):183–188.
18. Baskaran D, Aparicio-Ugarriza R, Ferri-Guerra J, et al. Is there an association between metformin exposure and frailty? Gerontol Geriatr Med 2020;6:2333721420924956; doi: 10.1177/2333721420924956
19. Cheng C, Lin CH, Tsai YW, et al. Type 2 diabetes and antidiabetic medications in relation to dementia diagnosis. J Gerontol A Biol Sci Med Sci 2014;69(10):1299–1305; doi: 10.1093/gerona/glu073
20. Ng TP, Feng L, Yap KB, et al. Long-term metformin usage and cognitive function among older adults with diabetes. J Alzheimers Dis 2014;41(1):61–68; doi: 10.3233/JAD-131901
21. Luchsinger JA, Perez T, Chang H, et al. Metformin in amnestic mild cognitive impairment: Results of a pilot randomized placebo controlled clinical trial. J Alzheimers Dis 2016;51(2):501–514; doi: 10.3233/JAD-150493
22. Scherrer JF, Morley JE, Salas J, et al. Association between metformin initiation and incident dementia among African American and White Veterans Health Administration Patients. Ann Fam Med 2019;17(4):352–362; doi: 10.1370/afm.2415
23. Masters MC, Yang J, Lake JE, et al. Diabetes mellitus is associated with declines in physical function among men with and without HIV. AIDS 2022;36(5):637–646; doi: 10.1097/QAD.0000000000003160
24. Yang J, Jacobson LP, Becker JT, et al. Impact of glycemic status on longitudinal cognitive performance in men with and without HIV infection. AIDS 2018;32(13):1849–1860; doi: 10.1097/QAD.0000000000001842
25. Erlandson KM, Ng DK, Jacobson LP, et al. Inflammation, immune activation, immunosenescence, and hormonal biomarkers in the frailty-related phenotype of men with or at risk for HIV infection. J Infect Dis 2017;215(2):228–237; doi: 10.1093/infdis/jiw523
26. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity 2013;39(4):633–645; doi: 10.1016/j.immuni.2013.10.001
27. Smurzynski M, Collier AC, Koletar SL, et al. AIDS clinical trials group longitudinal linked randomized trials (ALLRT): Rationale, design, and baseline characteristics. HIV Clin Trials 2008;9(4):269–282; doi: 10.1310/hct0904-269
28. Ellis RJ, Evans SR, Clifford DB, et al. Clinical validation of the NeuroScreen. J Neurovirol 2005;11(6):503–511; doi: 10.1080/13550280500384966
29. Erlandson KM, Wu K, Koletar SL, et al. Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis 2017;215(6):933–937; doi: 10.1093/infdis/jix063
30. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci 2001;56(3):M158-66; doi: 10.1093/gerona/56.3.m158
31. De Rekeneire N, Resnick HE, Schwartz AV, et al. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: The Health, Aging, and Body Composition study. Diabetes Care 2003;26(12):3257–3263.
32. Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. Diabetes Care 2000;23(9):1272–1277.

33. Kalyani RR, Tra Y, Yeh HC, et al. Quadriceps strength, quadriceps power, and gait speed in older U.S. adults with diabetes mellitus: Results from the National Health and Nutrition Examination Survey, 1999–2002. J Am Geriatr Soc 2013;61(5):769–775; doi: 10.1111/jgs.12204
34. Kuo CK, Lin LY, Yu YH, et al. Inverse association between insulin resistance and gait speed in nondiabetic older men: Results from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2002. BMC Geriatr 2009;9:49; doi: 10.1186/1471-2318-9-49
35. Okoro CA, Zhong Y, Ford ES, et al. Association between the metabolic syndrome and its components and gait speed among U.S. adults aged 50 years and older: A cross-sectional analysis. BMC Public Health 2006;6:282; doi: 10.1186/1471-2458-6-282
36. Fernando HJ, Cohen RA, Gullett JM, et al. Neurocognitive deficits in a cohort with class 2 and class 3 obesity: Contributions of type 2 diabetes and other comorbidities. Obesity (Silver Spring) 2019;27(7):1099–1106; doi: 10.1002/oby.22508
37. Khuder SS, Chen S, Letendre S, et al. Impaired insulin sensitivity is associated with worsening cognition in HIV-infected patients. Neurology 2019;92(12):e1344–e1353 doi: 10.1212/WNL.0000000000007125
38. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Arch Intern Med 2005;165(10):1179–1184; doi: 10.1001/archinte.165.10.1179
39. Hernandez-Romieu AC, Garg S, Rosenberg ES, et al. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. BMJ Open Diabetes Res Care 2017;5(1):e000304; doi: 10.1136/bmjdrc-2016-000304
40. Perez-Revuelta BI, Hettich MM, Ciociaro A, et al. Metformin lowers Ser-129 phosphorylated alpha-synuclein levels via mTOR-dependent protein phosphatase 2A activation. Cell Death Dis 2014;5:e1209; doi: 10.1038/cddis.2014.175
41. Cho K, Chung JY, Cho SK, et al. Antihyperglycemic mechanism of metformin occurs via the AMPK/LXR alpha/POMC pathway. Sci Rep 2015;5:8145; doi: 10.1038/srep08145
42. Duca FA, Cote CD, Rasmussen BA, et al. Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats. Nat Med 2015;21(5):506–511; doi: 10.1038/nm.3787
43. Gabuzda D, Jamieson BD, Collman RG, et al. Pathogenesis of aging and age-related comorbidities in people with HIV: Highlights from the HIV ACTION workshop. Pathog Immun 2020;5(1):143–174; doi: 10.20411/pai.v5i1.365
44. Planas D, Pagliuzza A, Ponte R, et al. LILAC pilot study: Effects of metformin on mTOR activation and HIV reservoir persistence during antiretroviral therapy. EBioMedicine 2021;65:103270; doi: 10.1016/j.ebiom.2021.103270
45. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab 2016;101(4):1754–1761; doi: 10.1210/jc.2015-3754
46. Porter KM, Ward M, Hughes CF, et al. Hyperglycemia and metformin use are associated with B vitamin deficiency and cognitive dysfunction in older adults. J Clin Endocrinol Metab 2019;104(10):4837–4847; doi: 10.1210/jc.2018-01791
47. Malin SK, Braun B. Impact of metformin on exercise-induced metabolic adaptations to lower type 2 diabetes risk. Exerc Sport Sci Rev 2016;44(1):4–11; doi: 10.1249/JES.0000000000000070
48. Walton RG, Dungan CM, Long DE, et al. Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: A randomized, double-blind, placebo-controlled, multicenter trial: The MASTERS trial. Aging Cell 2019;18(6):e13039; doi: 10.1111/acel.13039
49. Kulkarni AS, Peck BD, Walton RG, et al. Metformin alters skeletal muscle transcriptome adaptations to resistance training in older adults. Aging (Albany NY) 2020;12(20):19852–19866; doi: 10.18632/aging.104096
50. Barzilai N, Crandall JP, Kritchevsky SB, et al. Metformin as a tool to target aging. Cell Metab 2016;23(6):1060–1065; doi: 10.1016/j.cmet.2016.05.011

Address correspondence to:
Mary Clare Masters
Department of Internal Medicine
Northwestern University Feinberg School of Medicine
645 N. Michigan Avenue, Suite 900
Chicago, IL 60611
USA

E-mail: mary.masters@northwestern.edu