Aerobic Walking Exercise for Non-ambulatory Stroke Survivors

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Abstract

Stroke is a major cause of permanent disability worldwide. In the United States, stroke is the leading cause of disability and the 5th leading cause of death. The cost of care associated with stroke is expected to be $184 billion by 2030. After stroke, people commonly experience cardiovascular disease (metabolic syndrome, coronary artery disease, myocardial infarction, and hypertension), cognitive decline, sensorimotor disability, pulmonary dysfunction, psychological problems, and decreased bone health. The majority of past studies of rehabilitation therapy in stroke survivors have focused on recovery of sensorimotor function. Fewer studies have focused on cardiovascular, cardiopulmonary, and bone health after stroke, particularly in non-ambulatory individuals. The objective of this pilot project was to investigate the feasibility of an aerobic walking exercise program and its effects on the following outcome measures: cardiovascular risk factors, pulmonary function, and bone health in non-ambulatory stroke survivors.

In chapter one, we first reviewed the health sequelae after stroke focusing on cardiovascular, pulmonary, and bone health decline. We then reviewed the pharmacological and non-pharmacological (such as aerobic exercise) interventions for stroke survivors in general. We finally stated the significance of this dissertation project and listed aims and hypotheses.

In chapter two, a scoping review manuscript, we focused on the health benefits of aerobic walking exercise on cardiovascular, pulmonary, and bone health in non-ambulatory stroke survivors. We first reviewed the current state of clinical research findings of aerobic walking exercise in non-ambulatory stroke survivors. We summarized the health issues in the cardiopulmonary and skeletal systems in non-ambulatory stroke survivors. We reviewed the aerobic exercise guidelines for non-ambulatory stroke survivors. We then reviewed various studies reporting the pros and cons of body posture (standing vs. sitting) during exercise in terms of improvement or maintenance of health of the cardiopulmonary and skeletal systems in non-

ambulatory stroke survivors. We finally briefly reviewed the walking assistive device that makes walking exercise feasible for non-ambulatory stroke survivors.

In chapter three, we examined the feasibility and the effect of 8-weeks of aerobic walking exercise on lung function in non-ambulatory stroke survivors using a treadmill, body weight support system, and a gait training device. Lung function is compromised in stroke survivors, which may cause fatigue and exercise intolerance. We have completed a low intensity walking exercise program (30 minutes/session; three sessions/week for eight weeks) in 9 non-ambulatory stroke survivors (5 males, mean age 61.8 ± 13.6 years, 8 with ischemic stroke). We showed that 8-week of aerobic walking exercise was feasible, and compliance rate was 100% among the nine participants who completed the intervention. The attrition rate was10%. Before and after the intervention, vital capacity (VC) and forced vital capacity (FVC) using a spirometer were measured in eight of the participants. There were significant differences between pre- and post - intervention assessments in FVC (p= 0.09), percentage of predicted VC (p= 0.08), and percentage of predicted FVC (p= 0.08). The results are promising; however, future studies are needed.

In chapter four, we examined the effect of low intensity aerobic walking exercise on cardiovascular risk factors in non-ambulatory stroke survivors using a treadmill, body weight support system, and walking assistive device. Approximately 75% of stroke survivors are prone to having cardiovascular disease, the main cause of death in stroke survivors. However, few efforts have been made to control risks of cardiovascular diseases, especially in non-ambulatory stroke survivors. Nine non-ambulatory stroke survivors (age: 61.8 ± 13.6 years, 5 men, 8 with ischemic stroke) completed the aerobic walking exercise program (three sessions/week for eight weeks). Glycated hemoglobin (HbA1C), resting heart rate (rHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum level of low-density lipoprotein (LDL) were measured pre- and post-intervention. After the intervention, there were significant differences in HbA1c, rHR, SBP, and DBP. The results in this chapter suggest that the aerobic walking exercise may improve cardiovascular risk factors in non-ambulatory stroke survivors.

In chapter five, we aimed to examine changes after aerobic walking exercise in bone health in non-ambulatory stroke survivors using a treadmill, body weight support system, and a walking training device. Stroke survivors are at high risk of bone fracture. Compared to healthy people, stroke survivors are less active, and they tend to unload their bones on their affected lower limbs which rapidly increase bone loss. Non-ambulatory stroke survivors are largely losing bone health when compared to stroke survivors who walk independently. We recruited nine non-ambulatory stroke survivors (age: 61.8 ± 13.6 years, 5 men, 8 with ischemic stroke). They completed the aerobic walking exercise program (three sessions/week for eight weeks). Serum concentration of osteocalcin (OC) and carboxy-terminal telopeptide of type I collagen (ICTP) were measured pre- and post-intervention. OC increased significantly from 8.51±2.28 ng/ml to 9.39±2.97 ng/ml ($p < 0.1$). ICTP increased significantly from 4.45±2.58 ng/ml to 5.31±2.92 ng/ml ($p < 0.1$). The results suggest that the low intensity aerobic walking exercise may improve bone health by increasing bone formation markers. However, the initial severe disability of the participants and the nature of the aerobic walking exercise may initiate the bone remodeling process slowly.

In conclusion, past rehabilitation interventions for stroke survivors have not focused on controlling risks of pulmonary and cardiovascular diseases and bone loss, especially in strokes survivors who could not walk independently. To date, there have been very few clinical trials that attempted to examine the effects of aerobic walking exercise on risks of pulmonary function, cardiovascular disease, and bone health in non-ambulatory stroke survivors. The results of this dissertation project show that the low-intensity, aerobic walking exercise is feasible and might improve pulmonary function, cardiovascular health, and bone health in non-ambulatory stroke survivors.

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Chapter 1: Introduction

Stroke is a major cause of permanent disability worldwide.[1] In the United States, stroke is the leading cause of disability and the 5th leading cause of death. The cost of health care for stroke survivors is expected to be 184 billion by 2030.[2] Every 40 seconds in the United States there is a new case of stroke; and as a result, there are nearly 795,000 stroke cases each year, with 87% of those being ischemic strokes.[2] In addition to sensorimotor impairment, people after stroke commonly experience cardiovascular disease (i.e. metabolic syndrome, coronary artery disease, myocardial infarction, and hypertension), cognitive decline, sensorimotor disability, pulmonary dysfunction, psychological problems, and bone health declinations.[3-10] Previous studies have reported that pharmacological and non-pharmacological rehabilitation programs may help stroke survivors improve their motor skills and quality of life.[3,11,12] The majority of those studies have focused on recovery of sensorimotor function, while fewer studies have addressed health issues related to the cardiovascular system, pulmonary function, and bone health, particularly in non-ambulatory individuals.[13-15]

Diminished health after stroke

Stroke survivors often suffer from depression,[8,9] impaired cognition,[5,6] decreased balance control,[6] impaired upper limb motor function,[5] limitations in walking ability,[6,16,17] and negatively-altered muscle physiology in the affected limb.[18-20] In addition, stroke survivors commonly present with cardiovascular dysfunctions,[3,4,15,21-23] impairments in pulmonary function,[7] and deterioration in bone health.[10,24-26]

Cardiovascular dysfunction after stroke

Stroke survivors commonly present with cardiovascular dysfunction including, increased resting heart rate, increased insulin resistance, increased blood pressure, and altered lipids profile. About 75% of stoke survivors suffer from cardiac disease, a prominent cause of death after stroke.[3,4,15,21-23] Impairments in cardiovascular system reduce fitness level, which restricts stroke survivors from activities of daily living and predisposes them to cardiac diseases.[20,27-29] Compared to healthy people with sedentary lifestyles, stroke survivors present with a reduced fitness level by almost 50% and reduced cardiac output, which negatively affect engaging in daily physical activities.[30-32] The reduced fitness level is often related to an increased risk of cardiovascular diseases and mortality.[31-33] Stroke survivors often present with an elevated resting heart rate, due to prolonged bed rest and sedentary lifestyle, a risk factor for cardiac diseases such as myocardial infarction.[27,34] More than half of nondiabetic stroke survivors have insulin resistance during the subacute stage of stroke and are prone to diabetes mellitus.[19,35] Blood pressure is elevated in almost 80% of stroke survivors,[36] which is one of the risk factors for recurrent stroke and cardiac disease. More than half of hypertensive stroke survivors have uncontrolled blood pressure.[37-40] More than 50% of stroke survivors have impaired lipid profile, which is a risk factor for recurrent stroke.[36,40] In general, stroke survivors are at higher risk of stroke recurrence and/or cardiovascular disease, which may lead to severe disability or death.[19,20,35,41]

Impairments in pulmonary function after stroke

Stroke survivors often have impaired lung function, which may significantly hinder performance in daily activities and increase the risk of cardiovascular disease.[7] Stroke survivors have abnormal lung function and impaired breathing pattern due to weaknesses in respiratory muscles, sedentary lifestyle, damage to relevant neural pathways, and diaphragm hemiparesis.[20,42-45] For instance, stroke survivors had a lower tidal volume during submaximal exercise when compared to sedentary, healthy people.[46] Stroke survivors are at higher risk of pneumonia, aspiration, and sleep-disordered breathing, which might lead to stroke recurrence and other comorbidites.[45] Impairments in lung function predispose stroke survivors to rapid fatigue and exercise intolerance, which significantly limit their functional activities of daily living and their participation in rehabilitaiton programs.[42] Especially in those with severe stroke impairments, expiratory muscles are weak, which may lead to restrictive breathing.[47] Reduced lung function in stroke survivors increases the risk of recurrence of stroke [48] and risk of pulmonary infection due to an inability to efficiently clear the lungs from mucus.[49,50]

Declination of bone health after stroke

Stoke survivors often experience deterioration in bone health, especially in the affected limbs, which may increase the risk of bone fractures.[26] In stroke survivors, levels of bone formation markers are significantly lower and levels of bone resorption markers are significantly higher compared to healthy controls.[10] When compared to healthy individuals, osteoporosis is more common in stroke survivors even after a year of stroke onset.[51] Loss of bone health is largely noticed within six months of stroke onset and is associated with vascular rigidity, motor impairments, reduced fitness levels, and functional limitations.[10,24-26,52] While bone health deterioration occurs mostly during the subacute stage of stroke,[25,53] changes in bone health has not been systematically studied.

Treatment options for stroke survivors

Pharmacological interventions are popular among stroke survivors. Alteplase, antiplatelet, and antihypertensive drugs are administrated after stroke to control stroke symptoms and prevent stroke recurrence. Results of clinical trials are still uncertain, and those drugs should be used with caution since they are not appropriate for all stroke survivors.[11,12] Pharmacological and psychological treatments are implemented after stroke to deal with depression; however, the results regarding their effectiveness are still under debate.[54,55] In addition, some antidepressants may cause brain bleeds and osteoporosis.[56,57] Calcium and vitamin D supplementations are given to stroke survivors to maintain bone health; but their effectiveness is still controversial.[53]

Bisphosphonates and teriparatide are used to treat osteoporosis post-stroke; however, their side effects might limit their prescriptions.[53]

On the other hand, physical exercise has been recommended as a safe intervention during all stages after stroke. The effects of exercise on pulmonary function, cardiovascular function, and bone health after stroke are summarized in the following section.

Aerobic exercise (AE)

Benefits of AE during the subacute and chronic phases of stroke have been supported by research evidence. AE is feasible and improves cardiopulmonary fitness in people with mild or moderate subacute stroke.[58-62] AE enhances fitness level,[3,60,63] walking ability and distance, [3,60,63-66] vascular health in upper limbs,[61] and reduces resting heart rate [18] in people with mild and moderate subacute stroke. In a pilot study during the subacute stage, stroke survivors who received a combination of endurance, strength, and gait exercises improved their cardiopulmonary fitness and functional capacities compared to stroke survivors who received a standard rehabilitation program.[67]

AE improved maximum oxygen consumption,[5,6,8,29,68,69] walking distance and velocity, [5,6,29,69] peripheral and central blood flow,[70,71] right atrium and ventricular functions,[72] workload, [68] tolerance to exercise,[68] systolic blood pressure during exercise,[68] free fatty acid and lipid profiles,[73] and reduced insulin resistance [35] in people with mild and moderate chronic stroke. A significant relationship between improvement of exercise capacity and functional outcomes has been reported.[68] In a study conducted in ambulatory patients with chronic stroke, a combined rehabilitation program of muscle strengthening and AE enhanced lower limb strength, increased walking speed, and increased ability to climb a stair.[74] Physical exercise can increase loads on bones that may maintain or even improve bone health in chronic stroke survivors.[25] A 19-week

AE intervention improved the health of the femoral neck and tibia bone in people one year after stroke.[75,76]

Other exercise programs

Past studies have explored effects of other exercise programs in stroke survivors. In people with mild and moderate chronic stroke, tai chi improved endurance level,[77] motor function,[77] standing balance,[78,79] quality of life,[77,79] and reduced fall rates.[77] Yoga improved mobility [80] and balance,[80,81] but not anxiety and depression.[82] Water-based exercise improved fitness level,[83] walking speed [83,84] and lower limb strength [83,85] in chronic stroke survivors. Previous studies have also reported benefits of endurance,[86,87] resistance,[86,87] and balance exercise programs in stroke survivors.[87,88] Most of above-mentioned studies failed to evaluate their benefits on pulmonary, cardiovascular, and bone health in their participants.

Significance

Most rehabilitation interventions for stroke survivors are designed to improve sensorimotor function, but few efforts have been placed on controlling risks of pulmonary and cardiovascular diseases.[13-15] Lung function is compromised in stroke survivors and may cause fatigue and exercise intolerance.[42] About 75% of stroke survivors are prone to have cardiovascular diseases, the main cause of death in stroke survivors.[3,4,21-23] Stroke survivors are prone to diabetes mellitus due to an increase in fat tissues in their affected limbs.[19,35] Bone loss after stroke is associated with vascular elasticity, a marker of vascular system health,[52] and bone loss after stroke places stroke survivors at higher risk of bone fractures.[26] Previous studies have indicated that AE is feasible and may improve cardiopulmonary fitness,[58-61] vascular health, and reduce metabolic disorders in people after stroke.[33,61] AE, specifically, low intensity ergometer exercise, improved glucose tolerance and lipid profile in people with severe stroke.[89] However, many previous studies of AE have involved stroke survivors who could walk independently.[58-61]

In studies of those who were not able to walk, outcome measures of risk of cardiovascular diseases were not included.[32] Approximately 63% of stroke survivors cannot walk independently at stroke onset and 22 to 50% of them do not recover walking ability despite receiving rehabilitation.[90-97] In non-ambulatory stroke survivors, there is limited information regarding the effects of AE on risks of pulmonary function, cardiovascular disease, and bone health [58,89] even though they are at higher risk of these diseases.[59,89] In addition, severely impaired stroke survivors are readmitted to the hospital more and their healthcare services cost more when compared to stroke survivors with mild impairments.[98-100] Thus, it is important to provide non-ambulatory stroke survivors with an effective AE program to minimize the burden of healthcare costs and to prevent or, at least, alleviate secondary complications. Because of the development of new technology, it is now feasible to conduct an aerobic walking exercise program in non-ambulatory stroke survivors using a treadmill, body-weight support system, or a robotic assistive device.[31,32,101,102]

The proposed project seeks to examine the feasibility of an aerobic walking exercise program for improving pulmonary function, cardiovascular health, and bone health in non-ambulatory stroke survivors. Through the proposed project, we hope to find a way to decrease pulmonary impairments, cardiovascular risk factors, and deteriorations in bone health in non-ambulatory stroke survivors. Comorbidities after stroke, such as diabetes and hypertension, may significantly decrease life expectancy. In a recent study, life expectancy of diabetic patients was reported to be 11.1 years shorter when compared to a healthy population.[103] If the results of our project support our hypotheses, it may indicate that aerobic walking exercise might contribute to the improvement of quality of life and life expectancy of non-ambulatory stroke survivors.

Specific Aims and Statement of Hypotheses

Physical inactivity is often a consequence of sensorimotor impairment in stroke survivors and can lead to a decline in pulmonary, cardiovascular, and bone health. Partly due to physical inactivity, stroke survivors, especially non-ambulatory ones, are at much higher risk of pulmonary and cardiovascular diseases, bone loss, and recurrent stroke. Aerobic exercise, such as walking, is feasible to perform and effective for improving pulmonary, cardiovascular, and bone health in people after stroke. However, previous studies have targeted only those with mild/moderate impairments and the ability to walk independently. There is limited information regarding the effect of aerobic exercise interventions on the risks of pulmonary and cardiovascular diseases and bone loss in non-ambulatory stroke survivors. Despite intensive rehabilitation, 22 to 50% of stroke survivors remain non-ambulatory and are at high risk of additional pulmonary and cardiovascular diseases and/or bone health declines.

The **goal** of this dissertation project is to determine the feasibility of an assisted- aerobic walking exercise program for improving pulmonary function, cardiovascular risk factors, and bone health in non-ambulatory stroke survivors. Study participants will undergo an aerobic walking exercise program using a treadmill, body weight support system, and an assistive walking device,

Aim 1: To investigate the feasibility of eight weeks of aerobic exercise through an assisted-walking intervention in non-ambulatory stroke survivors.

We will report on feasibility data, which includes recruiting procedures (number of participants contacted, number of participants qualified, and number of participants enrolled), compliance rate, and attrition rate among study participants. In addition, we would include the participants' opinions regarding our intervention and the walking assistive device.

Aim 2: To investigate the effect of eight weeks of aerobic exercise through an assisted-walking intervention for improving pulmonary function in non-ambulatory stroke survivors.

Our hypotheses are that vital capacity (VC) (H1-2) and forced vital capacity (FVC) (H2-2) will be significantly increased after the completion of the intervention.

Aim 3: To investigate the effect of eight weeks of aerobic exercise through an assisted-walking intervention for improving cardiovascular risk factors in non-ambulatory stroke survivors.

Our *primary* hypotheses are that the level of glycated hemoglobin (HbA1c) (*P*H1-3) and resting heart rate (*P*H2-3) will be significantly decreased after the completion of the intervention.

Our *secondary* hypotheses are that resting blood pressure (*S*H1-3) and serum level of low-density lipoprotein (LDL) (*S*H2-3) will be significantly decreased after the completion of the intervention.

Aim 4: To investigate the effect of eight weeks of the aerobic exercise through an assisted-walking intervention for improving markers of bone health in non-ambulatory stroke survivors.

Our hypotheses are that serum level of osteocalcin (OC), a marker of bone formation, (H1-4) will be significantly increased and serum level of carboxy-terminal telopeptide of type I collagen (ICTP), a marker of bone resorption, (H2-4) will be significantly decreased after the completion of the intervention.

Exploratory aim: We will investigate the effect of the intervention on depression, walking ability, and balance in non-ambulatory stroke survivors. We will use Patient Health Questionnaire-9 (PHQ-9), Functional Ambulation Category (FAC), and the Berg Balance Scale

(BBS) to measure the depression, walking ability, and balance pre- and post-intervention, respectively.

References

1. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-1623.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
3. Stoller O, de Bruin ED, Knols RH, Hunt KJ. Effects of cardiovascular exercise early after stroke: systematic review and meta-analysis. *BMC neurology.* 2012;12:45.
4. Roth EJ. Heart disease in patients with stroke: incidence, impact, and implications for rehabilitation. Part 1: Classification and prevalence. *Archives of physical medicine and rehabilitation.* 1993;74(7):752-760.
5. Quaney BM, Boyd LA, McDowd JM, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation and neural repair.* 2009;23(9):879-885.
6. Globas C, Becker C, Cerny J, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabilitation and neural repair.* 2012;26(1):85-95.
7. Truelsen T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. *Int J Epidemiol.* 2001;30(1):145-151.
8. Lennon O, Carey A, Gaffney N, Stephenson J, Blake C. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clinical rehabilitation.* 2008;22(2):125-133.
9. Jorgensen TS, Wium-Andersen IK, Wium-Andersen MK, et al. Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients. *JAMA Psychiatry.* 2016.
10. Fisher A, Srikusalanukul W, Davis M, Smith P. Poststroke hip fracture: prevalence, clinical characteristics, mineral-bone metabolism, outcomes, and gaps in prevention. *Stroke research and treatment.* 2013;2013:641943.
11. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016;47(2):581-641.
12. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(1):315-353.
13. Wade D. Rehabilitation therapy after stroke. *Lancet.* 1999;354(9174):176-177.
14. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8(8):741-754.

15. Mackay-Lyons MJ, Makrides L. Exercise capacity early after stroke. *Archives of physical medicine and rehabilitation.* 2002;83(12):1697-1702.

16. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *The Cochrane database of systematic reviews.* 2016;3:CD003316.

17. Kelly JO, Kilbreath SL, Davis GM, Zeman B, Raymond J. Cardiorespiratory fitness and walking ability in subacute stroke patients. *Archives of physical medicine and rehabilitation.* 2003;84(12):1780-1785.

18. Katz-Leurer M, Shochina M, Carmeli E, Friedlander Y. The influence of early aerobic training on the functional capacity in patients with cerebrovascular accident at the subacute stage. *Archives of physical medicine and rehabilitation.* 2003;84(11):1609-1614.

19. Ivey FM, Hafer-Macko CE, Macko RF. Exercise training for cardiometabolic adaptation after stroke. *J Cardiopulm Rehabil Prev.* 2008;28(1):2-11.

20. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. *Stroke research and treatment.* 2012;2012:959120.

21. Delussu AS, Morone G, Iosa M, Bragoni M, Paolucci S, Traballesi M. Concurrent validity of Physiological Cost Index in walking over ground and during robotic training in subacute stroke patients. *BioMed research international.* 2014;2014:384896.

22. Lennon O, Blake C. Cardiac rehabilitation adapted to transient ischaemic attack and stroke (CRAFTS): a randomised controlled trial. *BMC neurology.* 2009;9:9.

23. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke. The Framingham study. *Stroke.* 1982;13(3):290-295.

24. Pang MY, Yang FZ, Lau RW, Cheng AQ, Li LS, Zhang M. Changes in bone density and geometry of the upper extremities after stroke: a case report. *Physiotherapy Canada Physiotherapie Canada.* 2012;64(1):88-97.

25. Borschmann K, Pang MY, Bernhardt J, Iuliano-Burns S. Stepping towards prevention of bone loss after stroke: a systematic review of the skeletal effects of physical activity after stroke. *International journal of stroke : official journal of the International Stroke Society.* 2012;7(4):330-335.

26. Pang MY, Eng JJ, McKay HA, Dawson AS. Reduced hip bone mineral density is related to physical fitness and leg lean mass in ambulatory individuals with chronic stroke. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2005;16(12):1769-1779.

27. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(8):2532-2553.

28. Pang MY, Eng JJ, Dawson AS, Gylfadottir S. The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: a meta-analysis. *Clinical rehabilitation.* 2006;20(2):97-111.

29. Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke.* 2005;36(10):2206-2211.

30. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: A mixed-methods systematic review and meta-analysis. *Brain Behav.* 2018;8(7):e01000.

31. Stoller O, de Bruin ED, Schindelholz M, Schuster-Amft C, de Bie RA, Hunt KJ. Efficacy of Feedback-Controlled Robotics-Assisted Treadmill Exercise to Improve Cardiovascular Fitness Early After Stroke: A Randomized Controlled Pilot Trial. *Journal of neurologic physical therapy : JNPT.* 2015;39(3):156-165.

32. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. *Neurorehabilitation and neural repair.* 2012;26(4):318-324.

33. Wang Z, Wang L, Fan H, et al. Adapted low intensity ergometer aerobic training for early and severely impaired stroke survivors: a pilot randomized controlled trial to explore its feasibility and efficacy. *Journal of physical therapy science.* 2014;26(9):1449-1454.

34. Wang A, Chen S, Wang C, et al. Resting heart rate and risk of cardiovascular diseases and all-cause death: the Kailuan study. *PLoS One.* 2014;9(10):e110985.

35. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke.* 2007;38(10):2752-2758.

36. Kopunek SP, Michael KM, Shaughnessy M, et al. Cardiovascular risk in survivors of stroke. *Am J Prev Med.* 2007;32(5):408-412.

37. Hornnes N, Larsen K, Boysen G. Little change of modifiable risk factors 1 year after stroke: a pilot study. *International journal of stroke : official journal of the International Stroke Society.* 2010;5(3):157-162.

38. Friday G, Alter M, Lai SM. Control of hypertension and risk of stroke recurrence. *Stroke.* 2002;33(11):2652-2657.

39. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. *Stroke.* 2014;45(8):2506-2513.

40. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Stroke.* 2004;35(5):1230-1240.

41. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *Jama.* 2000;284(22):2901-2906.

42. Ezeugwu VE, Olaogun M, Mbada CE, Adedoyin R. Comparative lung function performance of stroke survivors and age-matched and sex-matched controls. *Physiother Res Int.* 2013;18(4):212-219.

43. Vingerhoets F, Bogousslavsky J. Respiratory dysfunction in stroke. *Clin Chest Med.* 1994;15(4):729-737.

44. de Almeida IC, Clementino AC, Rocha EH, Brandao DC, Dornelas de Andrade A. Effects of hemiplegy on pulmonary function and diaphragmatic dome displacement. *Respiratory physiology & neurobiology.* 2011;178(2):196-201.

45. Rochester CL, Mohsenin V. Respiratory complications of stroke. *Semin Respir Crit Care Med.* 2002;23(3):248-260.

46. Sisante JF, Mattlage AE, Arena R, Rippee MA, Billinger SA. Decreased tidal volume may limit cardiopulmonary performance during exercise in subacute stroke. *J Cardiopulm Rehabil Prev.* 2015;35(5):334-341.

47. Fugl-Meyer AR, Linderholm H, Wilson AF. Restrictive ventilatory dysfunction in stroke: its relation to locomotor function. *Scand J Rehabil Med Suppl.* 1983;9:118-124.

48. van der Palen J, Rea TD, Manolio TA, et al. Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax.* 2004;59(12):1063-1067.

49. Jang SH, Bang HS. Effect of thoracic and cervical joint mobilization on pulmonary function in stroke patients. *Journal of physical therapy science.* 2016;28(1):257-260.

50. Kim J, Park JH, Yim J. Effects of respiratory muscle and endurance training using an individualized training device on the pulmonary function and exercise capacity in stroke patients. *Medical science monitor : international medical journal of experimental and clinical research.* 2014;20:2543-2549.

51. Tomasevic-Todorovic S, Simic-Panic D, Knezevic A, Demesi-Drljan C, Maric D, Hanna F. Osteoporosis in patients with stroke: A cross-sectional study. *Ann Indian Acad Neurol.* 2016;19(2):286-288.

52. Pang MY, Yang FZ, Jones AY. Vascular elasticity and grip strength are associated with bone health of the hemiparetic radius in people with chronic stroke: implications for rehabilitation. *Physical therapy.* 2013;93(6):774-785.

53. Huo K, Hashim SI, Yong KL, Su H, Qu QM. Impact and risk factors of post-stroke bone fracture. *World J Exp Med.* 2016;6(1):1-8.

54. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. *The Cochrane database of systematic reviews.* 2008(4):CD003437.

55. Chollet F, Acket B, Raposo N, Albucher JF, Loubinoux I, Pariente J. Use of antidepressant medications to improve outcomes after stroke. *Current neurology and neuroscience reports.* 2013;13(1):318.

56. Akoudad S, Aarts N, Noordam R, et al. Antidepressant Use Is Associated With an Increased Risk of Developing Microbleeds. *Stroke.* 2016;47(1):251-254.

57. Rizzoli R, Cooper C, Reginster JY, et al. Antidepressant medications and osteoporosis. *Bone.* 2012;51(3):606-613.

58. Stoller O, Schindelholz M, Bichsel L, et al. Feedback-controlled robotics-assisted treadmill exercise to assess and influence aerobic capacity early after stroke: a proof-of-concept study. *Disability and rehabilitation Assistive technology.* 2014;9(4):271-278.

59. Delussu AS, Morone G, Iosa M, Bragoni M, Traballesi M, Paolucci S. Physiological responses and energy cost of walking on the Gait Trainer with and without body weight support in subacute stroke patients. *Journal of neuroengineering and rehabilitation.* 2014;11:54.

60. Mackay-Lyons M, McDonald A, Matheson J, Eskes G, Klus MA. Dual effects of body-weight supported treadmill training on cardiovascular fitness and walking ability early after stroke: a randomized controlled trial. *Neurorehabilitation and neural repair.* 2013;27(7):644-653.

61. Billinger SA, Mattlage AE, Ashenden AL, Lentz AA, Harter G, Rippee MA. Aerobic exercise in subacute stroke improves cardiovascular health and physical performance. *Journal of neurologic physical therapy : JNPT.* 2012;36(4):159-165.

62. Bateman A, Culpan FJ, Pickering AD, Powell JH, Scott OM, Greenwood RJ. The effect of aerobic training on rehabilitation outcomes after recent severe brain injury: a randomized controlled evaluation. *Archives of physical medicine and rehabilitation.* 2001;82(2):174-182.

63. Duncan P, Studenski S, Richards L, et al. Randomized clinical trial of therapeutic exercise in subacute stroke. *Stroke.* 2003;34(9):2173-2180.

64. Mao YR, Lo WL, Lin Q, et al. The Effect of Body Weight Support Treadmill Training on Gait Recovery, Proximal Lower Limb Motor Pattern, and Balance in Patients with Subacute Stroke. *BioMed research international.* 2015;2015:175719.

65. Toledano-Zarhi A, Tanne D, Carmeli E, Katz-Leurer M. Feasibility, safety and efficacy of an early aerobic rehabilitation program for patients after minor ischemic stroke: A pilot randomized controlled trial. *NeuroRehabilitation.* 2011;28(2):85-90.

66. Eich HJ, Mach H, Werner C, Hesse S. Aerobic treadmill plus Bobath walking training improves walking in subacute stroke: a randomized controlled trial. *Clinical rehabilitation.* 2004;18(6):640-651.

67. Letombe A, Cornille C, Delahaye H, et al. Early post-stroke physical conditioning in hemiplegic patients: A preliminary study. *Annals of physical and rehabilitation medicine.* 2010;53(10):632-642.

68. Potempa K, Lopez M, Braun LT, Szidon JP, Fogg L, Tincknell T. Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke.* 1995;26(1):101-105.

69. Luft AR, Macko RF, Forrester LW, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke.* 2008;39(12):3341-3350.

70. Ivey FM, Hafer-Macko CE, Ryan AS, Macko RF. Impaired leg vasodilatory function after stroke: adaptations with treadmill exercise training. *Stroke.* 2010;41(12):2913-2917.

71. Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF. Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. *Stroke.* 2011;42(7):1994-2000.

72. Tang A, Eng JJ, Krassioukov AV, et al. Exercise-induced changes in cardiovascular function after stroke: a randomized controlled trial. *International journal of stroke : official journal of the International Stroke Society.* 2014;9(7):883-889.

73. Kim DY, Jung SY, Seo BD. Effect of exercise intervention on changes in free Fatty Acid levels and metabolic risk factors in stroke patients. *Journal of physical therapy science.* 2014;26(2):275-279.

74. Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B. Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. *Archives of physical medicine and rehabilitation.* 1999;80(10):1211-1218.

75. Pang MY, Eng JJ, Dawson AS, McKay HA, Harris JE. A community-based fitness and mobility exercise program for older adults with chronic stroke: a randomized, controlled trial. *J Am Geriatr Soc.* 2005;53(10):1667-1674.

76. Pang MY, Ashe MC, Eng JJ, McKay HA, Dawson AS. A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2006;17(11):1615-1625.

77. Taylor-Piliae RE, Hoke TM, Hepworth JT, Latt LD, Najafi B, Coull BM. Effect of Tai Chi on physical function, fall rates and quality of life among older stroke survivors. *Archives of physical medicine and rehabilitation.* 2014;95(5):816-824.

78. Au-Yeung SS, Hui-Chan CW, Tang JC. Short-form Tai Chi improves standing balance of people with chronic stroke. *Neurorehabilitation and neural repair.* 2009;23(5):515-522.

79. Kim H, Kim YL, Lee SM. Effects of therapeutic Tai Chi on balance, gait, and quality of life in chronic stroke patients. *Int J Rehabil Res.* 2015;38(2):156-161.

80. Bastille JV, Gill-Body KM. A yoga-based exercise program for people with chronic poststroke hemiparesis. *Physical therapy.* 2004;84(1):33-48.

81. Schmid AA, Van Puymbroeck M, Altenburger PA, et al. Poststroke balance improves with yoga: a pilot study. *Stroke.* 2012;43(9):2402-2407.

82. Chan W, Immink MA, Hillier S. Yoga and exercise for symptoms of depression and anxiety in people with poststroke disability: a randomized, controlled pilot trial. *Alternative therapies in health and medicine.* 2012;18(3):34-43.

83. Chu KS, Eng JJ, Dawson AS, Harris JE, Ozkaplan A, Gylfadottir S. Water-based exercise for cardiovascular fitness in people with chronic stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2004;85(6):870-874.

84. Park BS, Noh JW, Kim MY, et al. The effects of aquatic trunk exercise on gait and muscle activity in stroke patients: a randomized controlled pilot study. *Journal of physical therapy science.* 2015;27(11):3549-3553.

85. Lee DG, Jeong SK, Kim YD. Effects of underwater treadmill walking training on the peak torque of the knee in hemiplegic patients. *Journal of physical therapy science.* 2015;27(9):2871-2873.

86. Mead GE, Greig CA, Cunningham I, et al. Stroke: a randomized trial of exercise or relaxation. *J Am Geriatr Soc.* 2007;55(6):892-899.

87. Duncan P, Richards L, Wallace D, et al. A randomized, controlled pilot study of a home-based exercise program for individuals with mild and moderate stroke. *Stroke.* 1998;29(10):2055-2060.

88. Langhammer B, Stanghelle JK, Lindmark B. An evaluation of two different exercise regimes during the first year following stroke: a randomised controlled trial. *Physiotherapy theory and practice.* 2009;25(2):55-68.

89. Wang Z, Wang L, Fan H, Lu X, Wang T. Effect of low-intensity ergometer aerobic training on glucose tolerance in severely impaired nondiabetic stroke patients. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2014;23(3):e187-193.

90. Jorgensen HS, Nakayama H, Pedersen PM, Kammersgaard L, Raaschou HO, Olsen TS. Epidemiology of stroke-related disability. *Clin Geriatr Med.* 1999;15(4):785-799.

91. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Stroke. Neurologic and functional recovery the Copenhagen Stroke Study. *Phys Med Rehabil Clin N Am.* 1999;10(4):887-906.

92. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;76(1):27-32.

93. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;76(5):406-412.

94. Friedman PJ. Gait recovery after hemiplegic stroke. *Int Disabil Stud.* 1990;12(3):119-122.

95. Keenan MA, Perry J, Jordan C. Factors affecting balance and ambulation following stroke. *Clin Orthop Relat Res.* 1984(182):165-171.

96. Wade DT, Wood VA, Heller A, Maggs J, Langton Hewer R. Walking after stroke. Measurement and recovery over the first 3 months. *Scand J Rehabil Med.* 1987;19(1):25-30.

97. Chieffo R, Comi G, Leocani L. Noninvasive Neuromodulation in Poststroke Gait Disorders: Rationale, Feasibility, and State of the Art. *Neurorehabilitation and neural repair.* 2016;30(1):71-82.

98. Ottenbacher KJ, Graham JE, Ottenbacher AJ, et al. Hospital readmission in persons with stroke following postacute inpatient rehabilitation. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2012;67(8):875-881.

99. Thorngren M, Westling B. Utilization of health care resources after stroke. A population-based study of 258 hospitalized cases followed during the first year. *Acta neurologica Scandinavica.* 1991;84(4):303-310.

100. Tyagi S, Koh GC, Nan L, et al. Healthcare utilization and cost trajectories post-stroke: role of caregiver and stroke factors. *BMC Health Serv Res.* 2018;18(1):881.

101. Morone G, Bragoni M, Iosa M, et al. Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. *Neurorehabilitation and neural repair.* 2011;25(7):636-644.

102. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2006;87(10):1298-1304.

103. Jia H, Zack MM, Thompson WW. The effects of diabetes, hypertension, asthma, heart disease, and stroke on quality-adjusted life expectancy. *Value Health.* 2013;16(1):140-147.

Chapter 2: Potential benefits of aerobic walking exercise in non-ambulatory stroke survivors: A Scoping Review

Abstract

Stroke is the leading cause of long-term disability worldwide. After stroke, people commonly experience additional cardiovascular disease, cognitive declination, sensorimotor disability, pulmonary dysfunction, psychological problems, and bone health declinations. In stroke rehabilitation research, most of previous studies focused on recovery of sensorimotor function, with few studies examined outcomes in cardiopulmonary, cardiovascular, and bone health, particularly in non-ambulatory individuals who are at even higher risk of secondary complications. In this scoping review, we focused on the health benefits of aerobic walking exercise on cardiovascular, pulmonary, and bone health in non-ambulatory stroke survivors. We first reviewed the current state of clinical research findings of aerobic walking exercise in non-ambulatory stroke survivors. Then, we discussed the health issues in cardiopulmonary system and bones in non-ambulatory stroke survivors, and the aerobic exercise guidelines for non-ambulatory stroke survivors, and whether walking exercise was recommended for them. We discussed the exercise position (standing vs. sitting) to see which exercise position would be recommended to improve or at least maintain the health of cardiopulmonary system and bone in non-ambulatory stroke survivors. We finally discussed the walking assistive devices that make walking exercise feasible for non-ambulatory stroke survivors.

Key words: Stroke; non-ambulatory; walking; cardiovascular; cardiopulmonary; bone

Introduction

Stroke is the leading cause of long-term disability worldwide.[1] After stroke, people commonly experience additional cardiovascular disease (metabolic syndrome, coronary artery disease, myocardial infarction, and hypertension), cognitive decline, sensorimotor disability, pulmonary dysfunction, psychological problems, and bone health declinations.[2-9] Previous studies reported that pharmacological and non-pharmacological rehabilitation programs may help stroke survivors improve their motor skills and quality of life.[2,10,11] Many of those studies focused on recovery of sensorimotor function, while few studies focused on cardiopulmonary, cardiovascular, or bone health after stroke, particularly in non-ambulatory individuals [12-14] who are at high risk of secondary complications.[15,16] Cumulative findings of clinical studies have indicated that more than 50% of stroke survivors are disabled to some degree, despite intensive acute care and rehabilitation training.[17] Regarding gait impairment, about 57 to 63% of stroke survivors cannot walk independently at stroke onset and 22 to 50% of them remain non-ambulatory after intensive rehabilitation.[17-24] In addition, standard rehabilitation programs for stroke survivors with severe disabilities do not induce enough aerobic effect.[25,26] Non-ambulatory stroke survivors are physically inactive; and therefore, are at even higher risk of pulmonary dysfunction, cardiovascular disease, osteoporosis, and metabolic syndrome.[27-29] In this scoping review, we will review health benefits of aerobic walking exercise on the cardiopulmonary system and bones of stroke survivors who cannot walk independently. We will review the current state of clinical research findings of effect of aerobic exercise on pulmonary function, cardiovascular risk factors, and bone health in non-ambulatory stroke survivors. Then, we will discuss health issues in the cardiopulmonary system and bones in non-ambulatory stroke survivors and clinical guidelines as well as possible barriers for walking exercise in non-ambulatory stroke survivors. We will compare pros and cons of mode of exercise (standing vs sitting) in terms of improvement in cardiovascular, cardiopulmonary, and bone health through a review of indirect evidences, focusing on why we think walking exercise would be better for non-ambulatory stroke survivors. Finally, we will discuss recent development in technology that makes a walking exercise feasible for non-ambulatory stroke survivors in rehabilitation.

Methods

In this scoping review, we focused mainly on the effect of aerobic exercise on pulmonary function, cardiovascular risk factors, and bone health in non-ambulatory stroke survivors. MIDLINE (PubMed), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Physiotherapy Evidence Database (PEDro) were searched comprehensively to find clinical trials about the effect of aerobic exercise on cardiovascular risk factors, pulmonary function, and bone health in non-ambulatory stroke survivors. The following terms were utilized to identify potential studies: “non-ambulatory stroke”, “disabled stroke”, “wheelchair users”, “wheelchair bounded”, “dependent stroke”, “severely impaired stroke”, “heart rate”, “cardiovascular”, “blood pressure”, “lipid profile”, “low density lipoprotein”, “high density lipoprotein”, “total cholesterol”, “triglycerides”, “glucose”, “insulin”, “A1c”, “glycated hemoglobin”, “pulmonary function”, “respiratory function”, “lung function”, “respiratory indices”, “respiratory parameters”, “bone health”, “bone density”, “bone markers”, “aerobic exercise”, “walking training” “walking exercise” “gait training”, “locomotor training”, “robot-assisted”, “treadmill training”, “body weight support”, “ergometer”, “cycling”, “stationary bike”.

We included studies that were written in English, recruited non-ambulatory stroke survivors (≤ 2 on functional ambulation category (FAC) [30] or stated that participants were not able to walk or were totally dependent), utilized aerobic exercise, and reported on pulmonary function, cardiovascular risk factors, or bone health measurements. We excluded case reports, protocols articles, review articles, and cross-sectional studies.

After retrieving full articles, studies and references from selected studies were investigated to identify any study met our inclusion criteria by two reviewers (AA and RA) to make sure that all included studies met our selection criteria. WL was the third reviewer to resolve any disagreement in selection of studies.

Results

Figure 1 shows the searching and selection process of related studies. After searching the databases, 397 studies were found, and the number of those studies was decreased to 43 studies that included only non-ambulatory stroke survivors. Those 43 studies utilized either walking training [31-63] or exercise from seated position [16,64-66] for non-ambulatory stroke survivors. Of those 43 studies, only seven [16,36,38,47,56,60,66] studies met our selection criteria (table 1). The 27 of excluded studies did not include at least one of three primary measurements, i.e. pulmonary function, cardiovascular risk factors, or bone health measurements, but reported on walking ability, quality, or parameters,[31-35,37,39,48,49,51-54,58,59,61-63,67,68] motor function,[34,37,39,51,52,54,58,59,68] fitness level,[40] brain plasticity,[41] muscle thickness,[69] muscle activities,[64] and feasibility.[42,43,55] The reasons for excluding other 9 studies included non-ambulatory stroke survivors but did not meet our selection criteria such as cross sectional studies,[44,65] weight bearing assessment study,[45] walking assessment study,[46] study protocol,[70] not written in English, [71] jumping exercise intervention,[72] and case reports.[50,57]

Discussion

Aerobic exercise in non-ambulatory stroke survivors (with focus on measurements of cardiovascular risk factors, pulmonary function, and bone health)

There is limited information about the effects of aerobic exercise on pulmonary function, cardiovascular risk, and bone health in non-ambulatory stroke survivors. We found only seven studies [16,36,38,47,56,60,66] that focused on non-ambulatory stroke survivors and reported outcomes in cardiovascular risk factors (table 1). None of these selected studies [16,36,38,47,56,60,66] reported results on pulmonary function or bone health. In a Cochrane review published in 2016,[73] only two trials [16,59] out of 58 trials focused on non-ambulatory stroke survivors. In 2017, a meta-analysis [74] that investigated the effect of aerobic exercise on cardiovascular risk following stroke included only one study [16] in non-ambulatory stroke survivors.

All selected studies [16,36,38,47,56,60,66] were conducted during acute or subacute phases after stroke, and neither of them included any variable regarding pulmonary function or bone health. Those selected studies reported on some of cardiovascular risk factors such as blood pressure,[36,47,56] heart rate,[16,36,38,47,56,60] both high- (HDL) and low-density lipoprotein (LDL) cholesterols,[16,66] total triglycerides,[16,66] insulin and glucose levels,[16,66] and brachial–ankle pulse wave velocity [47] which is an indicator of arterial stiffness (table 1).

In all selected studies,[16,36,38,47,56,60,66] statistically significant differences between groups were reported in peak heart rate,[60] fasting insulin,[16] 2-hour glucose level,[16,66] homeostasis model assessment–insulin resistance,[16,66] glucose tolerance states,[16] total triglycerides,[16] and brachial–ankle pulse wave velocity.[47] On the other hand, non-statistically significant differences between groups were found in resting heart rate,[16,36,47,60] peak heart rate, [16,36,38,47,56,66] resting blood pressure,[47] peak blood pressure,[36,47,56] HDL cholesterol,[16,66] LDL cholesterol,[16,66] fasting insulin,[66] fasting glucose,[66] and total triglycerides.[66]

The lack of improvement in resting heart rate,[16,36,47,60] peak heart rate,[16,36,38,47,56,66] resting blood pressure,[47] peak blood pressure,[36,47,56] and lipid profile [16,66] may be due to following reasons. First, the participants in those studies [16,36,47] were within less than one month [36,47] or less than six months [16] post stroke while their resting heart rate and resting blood pressure were still within the normal range. Second, medications that might affect peak heart rate or peak blood pressure were not controlled,[36,38,47,56] which might significantly influence their results. In addition, it is recommended that a minimum of 8 weeks of aerobic exercise is needed to improve cardiovascular health after stroke.[75] The training period in those studies [16,36,47,60,66] (2 to 6 weeks) may be too short to induce significant differences in outcome measurements. Last but not least, the lokomat or locomotor walking training,[36,47,60] treadmill training with body weight support,[38] or ergometer aerobic training [16,66] might provide insufficient challenge during the training to cardiovascular system of the participants.

Health Issues in the Cardiopulmonary System and Bone in Non-ambulatory Stroke Survivors

Non-ambulatory stroke survivors commonly present with serious cardiovascular complications. Compared to healthy people with sedentary lifestyle, stroke survivors present with a reduced fitness level by almost 50% and reduced cardiac output, which affect negatively their engaging in daily physical activities.[36,40,76] The reduced fitness level is often related to an increase in risk of cardiovascular diseases and mortality.[36,40,66] Hypertension is prevalent in almost 80% of stroke survivors after they discharged from the hospital.[77] Non-ambulatory stroke survivors are at higher risk of cardiovascular disease compared to ambulatory stroke survivors.[76] Non-ambulatory stroke survivors are prone to deep vein thrombosis, which might cause sudden death once it reaches the lungs or heart.[78] Furthermore, non-ambulatory stroke survivors who did not have diabetes before stroke onset are prone to develop diabetes mellitus.[16] Non-ambulatory stroke survivors are at high risk of glucose intolerance, which can increase the risk of atherosclerosis, myocardial infarction, and recurrent stroke.[16] Although 75% of stroke survivors are prone to cardiovascular disease that is a prominent cause of death post-stroke,[79] information regarding cardiovascular health in non-ambulatory stroke survivors is relatively limited.[14,76]

Non-ambulatory stroke survivors often exhibit decline in lung function. Non-ambulatory stroke survivors are physically inactive with a sedentary lifestyle [29] which leads to poor lung function.[80] Impaired lung function in stroke survivors usually hinders performance in daily activities and increases the risk of cardiovascular disease.[6] Abnormal lung function and impaired breathing in stroke survivors may be due to weaknesses in respiratory muscles, sedentary lifestyle, damage to relevant neural pathways, and diaphragm hemiparesis.[81-84] For instance, stroke survivors during subacute stage showed a lower tidal volume during submaximal exercise when compared to sedentary healthy people.[85] Impairments in lung function predispose stroke survivors to rapid fatigue and exercise intolerance, which significantly limit their functional activities of daily living and their participation in rehabilitaiton programs.[81] Impairments in lung function also increase the risk of recurrence of stroke [86] and risk of pulmonary infection because of the inability to clear up the lungs efficiently of mucus.[87,88]

Non-ambulatory stroke survivors might lose their bone density and bone mass rapidly. Due to a decrease in limb loading, non-ambulatory stroke survivors are at higher risk of rapid bone loss when compared to stroke survivors who are able to walk.[89] In general, stroke survivors often experience deterioration in bone health, especially in the affected limbs, which increases the risk of bone fractures.[90] In stroke survivors, bone formation markers are significantly lower and bone resorption markers are significantly higher compared to healthy adults.[9] Osteoporosis is common in stroke survivors during the first year after stroke onset when compared to healthy individuals.[91] Loss of bone health is noticed largely within six months of stroke onset and is associated with vascular rigidity, motor impairments, reduced fitness level, and functional limitations.[9,90,92-94] In a rodent model of ischemic stroke using female rat, bone resorption and osteoclast activities were increased in the femoral and tibial bones of the hemiplegic sides one week post stroke.[95] N-terminal propeptide of type 1 procollagen, a bone formation marker, was significantly decreased in male rats after 28 days of stroke onset. However, cortical and total bone volumes were higher in control male rats compared to rats with stroke.[96]

Although aerobic walking exercise may possess the potential for improvement in cardiovascular systems in non-ambulatory stroke survivors, it has not been recommended by exercise guidelines. Current guidelines for adult stroke rehabilitation proposed by the American Heart Association recognize the promising results of walking exercise in non-ambulatory stroke survivors, but did not strongly recommend its clinical application due to currently insufficient supporting evidence.[97,98] The guidelines strongly encourage future research to explore the broader application and effectiveness of assisted gait training to benefit cardiovascular and pulmonary systems after stroke.

Why Aerobic Walking Exercise?

Due to the limited number of clinical studies, we are unable to fully evaluate the potential for aerobic walking exercise to improve cardiopulmonary and bone health in non-ambulatory stroke survivors. Even though direct evidence from clinical trials are lacking, we present information on several important aspects in which indirect evidence strongly implies there are potential benefits of aerobic walking exercise for cardiopulmonary and bone health in non-ambulatory stroke survivors.

Aerobic walking exercise may improve cardiovascular health in non-ambulatory stroke survivors through elevation of heart rate during exercise. A previous study reported that walking exercise prevented diabetes in stroke survivors.[99] Non-ambulatory stroke survivors may develop deep vein thrombosis during the first few months after stroke onset.[78,100] Ivey et al.[101] observed that a single session of low intensity aerobic walking exercise immediately enhanced endogenous fibrinolysis in chronic stroke patients. Increased fibrinolysis can reduce the risk of deep vein thrombosis because it breaks down fibrin of blood clots. Exercise in an upright position (i.e. walking) is optimal for increasing heart rate, which is essential for beneficial outcomes.[102] When compared to lying and sitting, standing can significantly elevate heart rate. Due to gravitational force, standing causes a decrease in venous return and leads to an elevated heart rate in order to maintain cardiac output.[103] During stroke rehabilitation, a positive correlation has been reported between time spent in the aerobic heart rate zone and time spent standing. In contrast, a negative correlation was found between time spent in the aerobic heart rate zone and time spent sitting.[104] An increased heart rate raises blood pressure and shear stress against the vessel walls and enhances vessel health and vasodilation function.[105]

Aerobic walking exercise may improve cardiopulmonary fitness level in non-ambulatory stroke survivors through activation of lower limb muscles. Exercise targeting lower limb muscles leads to greater gains in fitness level compared to exercise of upper body because leg muscles are larger and more powerful.[83,106] Past studies reported that aerobic walking exercise improves cardiopulmonary fitness level in stroke survivors.[15,107] Passive walking, using robot-assisted treadmill training, increases oxygen uptake due to contraction of large leg muscles in the unaffected side.[108] During assisted walking, muscles in the affected lower limb are activated through central pattern generators (CPGs) in the spinal cord. CPGs are stimulated by loading on hip joint and are guided by afferent inputs from lower limbs' sensory receptors.[109] The maximum oxygen uptake in stroke survivors is 50% lower when compared to healthy and sedentary peers with similar ages. Increasing oxygen uptake is crucial for stroke survivors in performing their daily living activities.[36,40,76,83]

Past studies in healthy people and individuals with other health conditions have reported that aerobic walking can stress the cardiovascular and cardiopulmonary systems more effectively than exercise in sitting position. In a cardiopulmonary stress test controlled at 85% of the age-predicted maximum heart rate, healthy adults exhibited a significantly higher heart rate, blood pressure, and oxygen consumption when tested on the treadmill compared to an arm ergometry.[110] In individuals with heart failure, the maximal cardiopulmonary test on a treadmill resulted in higher heart rate reserve and peak oxygen consumption when compared to tests on a cycloergometer.[111] In an incremental test, patients with incomplete spinal cord injury showed a higher maximum oxygen consumption when tested using a robot-assisted treadmill compared to an arm ergometer.[112] Walking may be a better modality than sitting for stressing the cardiovascular and cardiopulmonary systems, due to an increase in the myocardium oxygen demand [110] and the activation of larger muscles.[112]

Aerobic walking may help maintain normal physiology of the muscles in the trunk and lower limbs of people after stroke. Non-ambulatory stroke survivors are usually physically inactive,[16] which leads to a decrease in muscle oxidative capacity [75,113] and transformation of muscle fibers to type II that are easily fatigable and resist glucose uptake due to lower sensitivity to insulin.[75,83,113] Aerobic walking exercise can provide the needed loading to prevent lower limb muscle atrophy [114] and improve trunk muscle function and balance control.[113,115]

Aerobic walking exercise may stimulate sensory and motor neurons in the central nervous system through afferent inputs to induce neuroplasticity in the brain and enhance CPGs in spinal cord, which may result in improvement in capability for locomotion and daily living function in stroke survivors.[24,27,109,113,116-118] Aerobic walking exercise using a treadmill increases the neural activity in the premotor cortex of healthy subjects and in the affected and unaffected hemispheres of stroke survivors.[117,118] In addition, basic walking is partially regulated by CPGs located in the spinal cord, which is intact in stroke survivors.[109,118] Inputs into CPGs from both supraspinal centers and proprioceptive sensors located in muscles and joints of lower limbs are important for producing a high quality walking pattern.[109,118] For instance, loading on the hip joints and extensor muscles of lower limbs facilitated walking in healthy adults and people with spinal cord injury, due to enhanced activity of CPGs.[109] Walking velocity and endurance were increased after walking exercise using treadmill in ambulatory stroke survivors.[119] Some of non-ambulatory stroke survivors may regain walking ability after a walking exercise program.[24] For instance, some non-ambulatory stroke survivors regained walking ability after 4 weeks of treadmill walking using a body-weight support system during the early stage of stroke onset.[120]

Furthermore, aerobic walking exercise may improve bone health in non-ambulatory stroke survivors. Loading exercise such as walking is effective in preventing bone loss.[114] Loading on bones during walking helps maintain bone density by stimulating biological factors of bone formation.[89,114] In a study of ambulatory stroke survivors, those who completed 19 weeks of aerobic walking and weight bearing exercises improved their bone health compared to participants in a control group who completed 19 weeks of seated, upper limb exercise.[121,122] Through a comparison of measured bone density between runners and cyclists, past studies demonstrated the role of loading in maintaining bone quality.[123,124] In people with paraplegic spinal cord injury, a group who completed 12 weeks (3 sessions/week) of walking training significantly increased biomarkers of bone formation and bone density of the femur and lumbar spine when compared to the group that received regular exercises.[125] Furthermore, in people with quadriplegic spinal cord injury, a group who completed 6 months (2 sessions/week) of treadmill walking exercise showed a significant increase in biomarkers of bone formation and decrease in biomarkers of bone resorption when compared to a group who received sitting exercise.[126] To the best of our knowledge, no study has investigated the effect of walking on bone health in non-ambulatory stroke survivors; and therefore, future studies on the issue are needed.

Past studies in the last two decades have demonstrated that even periodic standing breaks from prolonged sitting can provide health benefits in the cardiovascular system. The American College of Sports Medicine recommends that people with a sedentary lifestyle break up their prolonged sitting time with periodic standing in order to reduce the risk of metabolic disorders.[127] Standing decreases the risk of obesity [128] and level of plasma glucose [129] in healthy office workers. Standing requires continuous contraction of trunk and lower limb muscles, which may lead to an improvement in blood glucose levels and lipid profiles.[129-131] In overweight and obese adults with sedentary lifestyles, interrupting prolonged sitting time with low intensity walking significantly decreased systolic and diastolic blood pressure.[132]

Aerobic walking exercise can improve the mood of people who sit a prolonged amount of time in their jobs or leisure, which may extend to non-ambulatory stroke survivors. In healthy office workers, breaking up sitting time by using the sit-stand desk for 4 weeks improved mood.[133] In chronic stroke survivors, mood was correlated with time spent on their feet, indicating that higher levels of depression led to less time spent standing.[134] In addition, 12 sessions of walking exercise decreased depression in chronic stroke survivors.[135] 12 weeks (3 times/week) of walking improved the mood of women with breast cancer receiving chemotherapy when compared to not walking.[136] Since mood disturbances are one of the common symptoms affecting stroke survivors [137] and are more common in stroke survivors who have moderate to severe motor disabilities,[138] we believe that a walking exercise program would improve the mood of non-ambulatory stroke survivors and may lead to the improvement in their interactions with other people.[135,139]

Current Development in Technology Making Aerobic Walking Exercise Feasible

Recent developments in new technology, especially in body-weight support and robot-assisted gait training, have made walking exercise feasible for non-ambulatory stroke survivors.[36,40,140,141] For instance, in a past study non-ambulatory subacute stroke survivors were trained using a robot-assisted treadmill for four weeks.[40] In a different study, the investigators recruited subacute stroke survivors and trained them using robot-assistance for four weeks.[140] In a recent systematic review and meta-analysis,[76] 11 studies used 4 different assistive walking devices during walking training for non-ambulatory stroke survivors. Treadmill gait training with some type of assistive devices have had no report of any adverse events. Although walking exercise is feasible for non-ambulatory stroke survivors, they might not engage in walking in community settings due to a lack of assistive devices. Assistive devices are expensive and require professional therapist to operate them.[76] Thus, we believe it is important to provide non-ambulatory stroke survivors with access to walking assistive devices and body-weight support systems by developing affordable training devices through future research and development.

Conclusion

Past rehabilitation interventions for stroke survivors have not focused on controlling risks of cardiovascular and cardiopulmonary diseases, especially in strokes survivors who cannot walk independently. To date, there has been a limited number of clinical trials that have attempted to examine the effects of aerobic walking exercise on risks of pulmonary function, cardiovascular disease, and bone health in non-ambulatory stroke survivors. However, a large number of indirect, supporting evidence in past studies strongly indicate the great potential of walking in non-ambulatory stroke survivors. Thus, future studies should focus on the feasibility, efficacy, and revision of guidelines regarding aerobic walking and its effects on cardiopulmonary and bone health in non-ambulatory stroke survivors.

Table 1: Details about studies which met selection criteria.

Reference	Level of walking	Time since stroke	Intervention group	Control group	Results of variables related to CV risk factors, pulmonary function, or bone health
Teixeira et al. [56]	FAC ≤ 2	Within 4 weeks post stroke	Received walking training with body weight support system (20 minutes/day for 2 to 3 weeks) + regular physical therapy	Received daily regular physical therapy for 2 to 3 weeks	No statistically significant changes in peak systolic and diastolic blood pressure, and peak heart rate between groups
Mehrholz et al. [60]	FAC ≤ 2	Within 6 weeks post stroke	Received repetitive locomotor training (20 minutes) + conventional physical therapy (25 minutes), (5 days/week for 4 weeks)	Received conventional physical therapy (45 minutes), (5 days/week for 4 weeks)	No statistically significant changes in resting heart rate between groups. Statistically significant changes found in peak heart rate between groups
Chang et al. [36]	FAC < 2	Within a month of stroke onset	Received lokomat walking training (40 minutes) + conventional physical therapy (60 minutes), (5 days/week for 2 weeks)	Received daily conventional physical therapy (100 minutes), (5 days/week for 2 weeks)	No statistically significant changes in resting and peak heart rate, and peak systolic and diastolic blood pressure between groups
Hoyer et al. [38]	FAC ≤ 2	1 to 6 months post stroke	Received Treadmill training with body weight support (30 minutes) + conventional physical	Received daily conventional physical therapy and overground walking training (60 minutes), (5	No statistically significant changes in peak heart rate between groups

			therapy (30 minutes), (5 days/week for 4 weeks), then (1 to2 sessions/week for 6 weeks) + overground walking training in the days without treadmill	days/week for10 weeks)	
Wang et al. [16]	Unable to walk even with walk aids	1 to 6 months post stroke	Received low-intensity ergometer aerobic training (3 sessions/week) + regular rehabilitation program (5 sessions/week) for 6 weeks	Received regular rehabilitation program (5 sessions/week) for 6 weeks	Fasting insulin, 2-hour glucose level, homeostasis model assessment–insulin resistance, glucose tolerance states, and total triglycerides were improved significantly in intervention group. No statistically significant changes found in resting and peak heart rate, HDL cholesterol, and LDL cholesterol between groups
Wang et al. [66]	Unable to walk with any walk aid2	2 to 6 weeks post stroke	Received low-intensity ergometer aerobic training (3 sessions/week) + regular rehabilitation program (5 sessions/week) for 6 weeks	Received regular rehabilitation program (5 sessions/week) for 6 weeks	2-hour glucose level and homeostasis model assessment–insulin resistance were improved significantly in intervention group. No statistically significant changes found in fasting insulin, fasting glucose, total triglycerides, HDL cholesterol, LDL cholesterol, peak

					heart rate between groups.
Han et al. [47]	FAC <2	Within a month of stroke onset	Received robot-assisted gait training (30 minutes) + regular rehabilitation program (30 minutes), (5 sessions/week for 4 weeks)	Received regular rehabilitation program (60 minutes), (5 sessions/week for 4 weeks)	Brachial–ankle pulse wave velocity was significantly reduced in intervention group. No statistically significant changes found in resting and peak heart rate, and resting and peak systolic and diastolic blood pressure between groups

CV: cardiovascular, FAC: Functional ambulation category, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

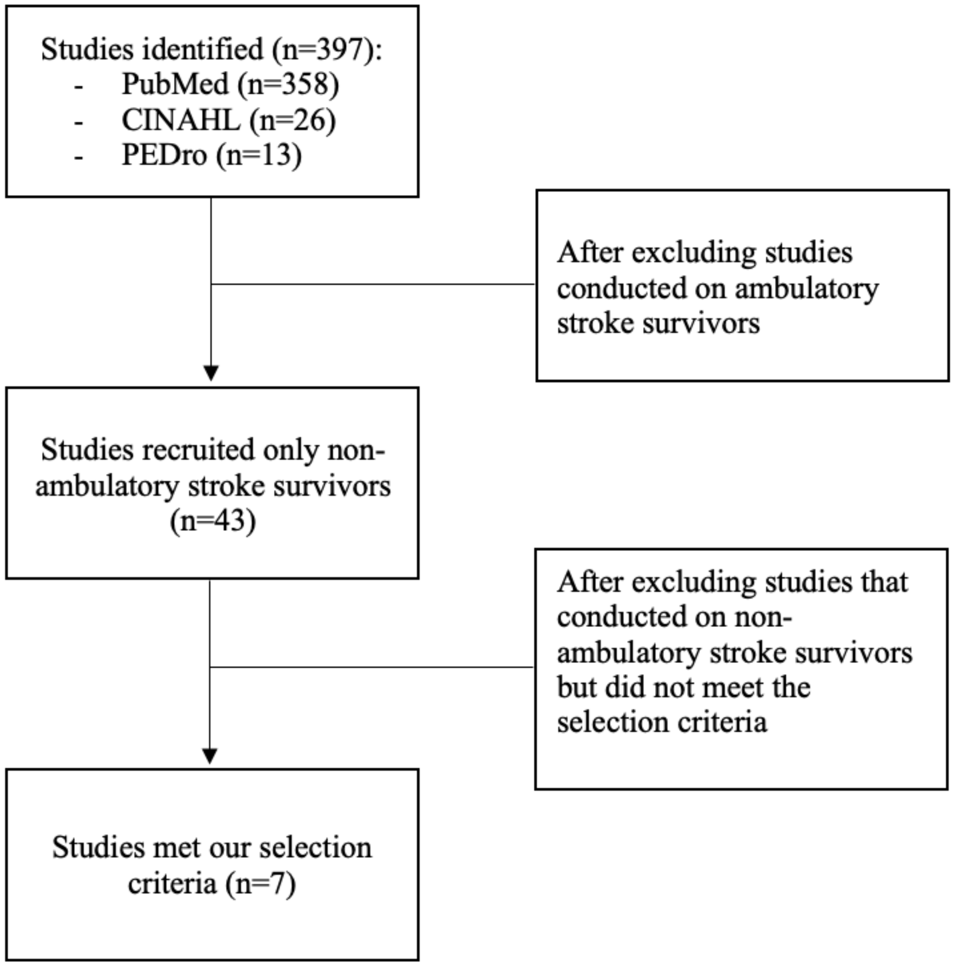

Figure 1: Studies selection process.

References

1. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-1623.
2. Stoller O, de Bruin ED, Knols RH, Hunt KJ. Effects of cardiovascular exercise early after stroke: systematic review and meta-analysis. *BMC neurology.* 2012;12:45.
3. Roth EJ. Heart disease in patients with stroke: incidence, impact, and implications for rehabilitation. Part 1: Classification and prevalence. *Archives of physical medicine and rehabilitation.* 1993;74(7):752-760.
4. Quaney BM, Boyd LA, McDowd JM, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation and neural repair.* 2009;23(9):879-885.
5. Globas C, Becker C, Cerny J, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabilitation and neural repair.* 2012;26(1):85-95.
6. Truelsen T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. *Int J Epidemiol.* 2001;30(1):145-151.
7. Lennon O, Carey A, Gaffney N, Stephenson J, Blake C. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clinical rehabilitation.* 2008;22(2):125-133.
8. Jorgensen TS, Wium-Andersen IK, Wium-Andersen MK, et al. Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients. *JAMA Psychiatry.* 2016.
9. Fisher A, Srikusalanukul W, Davis M, Smith P. Poststroke hip fracture: prevalence, clinical characteristics, mineral-bone metabolism, outcomes, and gaps in prevention. *Stroke research and treatment.* 2013;2013:641943.
10. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016;47(2):581-641.
11. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(1):315-353.
12. Wade D. Rehabilitation therapy after stroke. *Lancet.* 1999;354(9174):176-177.
13. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8(8):741-754.
14. Mackay-Lyons MJ, Makrides L. Exercise capacity early after stroke. *Archives of physical medicine and rehabilitation.* 2002;83(12):1697-1702.

15. Delussu AS, Morone G, Iosa M, Bragoni M, Traballesi M, Paolucci S. Physiological responses and energy cost of walking on the Gait Trainer with and without body weight support in subacute stroke patients. *Journal of neuroengineering and rehabilitation.* 2014;11:54.

16. Wang Z, Wang L, Fan H, Lu X, Wang T. Effect of low-intensity ergometer aerobic training on glucose tolerance in severely impaired nondiabetic stroke patients. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2014;23(3):e187-193.

17. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Stroke. Neurologic and functional recovery the Copenhagen Stroke Study. *Phys Med Rehabil Clin N Am.* 1999;10(4):887-906.

18. Jorgensen HS, Nakayama H, Pedersen PM, Kammersgaard L, Raaschou HO, Olsen TS. Epidemiology of stroke-related disability. *Clin Geriatr Med.* 1999;15(4):785-799.

19. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;76(1):27-32.

20. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;76(5):406-412.

21. Friedman PJ. Gait recovery after hemiplegic stroke. *Int Disabil Stud.* 1990;12(3):119-122.

22. Keenan MA, Perry J, Jordan C. Factors affecting balance and ambulation following stroke. *Clin Orthop Relat Res.* 1984(182):165-171.

23. Wade DT, Wood VA, Heller A, Maggs J, Langton Hewer R. Walking after stroke. Measurement and recovery over the first 3 months. *Scand J Rehabil Med.* 1987;19(1):25-30.

24. Chieffo R, Comi G, Leocani L. Noninvasive Neuromodulation in Poststroke Gait Disorders: Rationale, Feasibility, and State of the Art. *Neurorehabilitation and neural repair.* 2016;30(1):71-82.

25. Jin H, Jiang Y, Wei Q, Chen L, Ma G. Effects of aerobic cycling training on cardiovascular fitness and heart rate recovery in patients with chronic stroke. *NeuroRehabilitation.* 2013;32(2):327-335.

26. Ivey FM, Hafer-Macko CE, Macko RF. Exercise rehabilitation after stroke. *NeuroRx.* 2006;3(4):439-450.

27. Luft AR, Macko RF, Forrester LW, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke.* 2008;39(12):3341-3350.

28. Kim DY, Jung SY, Seo BD. Effect of exercise intervention on changes in free Fatty Acid levels and metabolic risk factors in stroke patients. *Journal of physical therapy science.* 2014;26(2):275-279.

29. Fini NA, Bernhardt J, Holland AE. What is the relationship between physical activity and cardiovascular risk factors in stroke survivors post completion of rehabilitation? Protocol for a longitudinal study. *BMJ Open.* 2017;7(11):e019193.

30. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Physical therapy.* 1986;66(10):1530-1539.

31. Mayr A, Quirbach E, Picelli A, Kofler M, Smania N, Saltuari L. Early robot-assisted gait retraining in non-ambulatory patients with stroke: a single blind randomized controlled trial. *European journal of physical and rehabilitation medicine.* 2018;54(6):819-826.

32. Kim SJ, Lee HJ, Hwang SW, et al. Clinical Characteristics of Proper Robot-Assisted Gait Training Group in Non-ambulatory Subacute Stroke Patients. *Annals of rehabilitation medicine.* 2016;40(2):183-189.

33. Dean CM, Ada L, Bampton J, Morris ME, Katrak PH, Potts S. Treadmill walking with body weight support in subacute non-ambulatory stroke improves walking capacity more than overground walking: a randomised trial. *Journal of physiotherapy.* 2010;56(2):97-103.

34. Pohl M, Werner C, Holzgraefe M, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). *Clinical rehabilitation.* 2007;21(1):17-27.

35. Werner C, Bardeleben A, Mauritz KH, Kirker S, Hesse S. Treadmill training with partial body weight support and physiotherapy in stroke patients: a preliminary comparison. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* 2002;9(6):639-644.

36. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. *Neurorehabilitation and neural repair.* 2012;26(4):318-324.

37. Cho DY, Park SW, Lee MJ, Park DS, Kim EJ. Effects of robot-assisted gait training on the balance and gait of chronic stroke patients: focus on dependent ambulators. *Journal of physical therapy science.* 2015;27(10):3053-3057.

38. Hoyer E, Jahnsen R, Stanghelle JK, Strand LI. Body weight supported treadmill training versus traditional training in patients dependent on walking assistance after stroke: a randomized controlled trial. *Disability and rehabilitation.* 2012;34(3):210-219.

39. Freivogel S, Schmalohr D, Mehrholz J. Improved walking ability and reduced therapeutic stress with an electromechanical gait device. *Journal of rehabilitation medicine.* 2009;41(9):734-739.

40. Stoller O, de Bruin ED, Schindelholz M, Schuster-Amft C, de Bie RA, Hunt KJ. Efficacy of Feedback-Controlled Robotics-Assisted Treadmill Exercise to Improve Cardiovascular Fitness Early After Stroke: A Randomized Controlled Pilot Trial. *Journal of neurologic physical therapy : JNPT.* 2015;39(3):156-165.

41. Yang HE, Kyeong S, Lee SH, et al. Structural and functional improvements due to robot-assisted gait training in the stroke-injured brain. *Neuroscience letters.* 2017;637:114-119.

42. Nilsson A, Vreede KS, Haglund V, Kawamoto H, Sankai Y, Borg J. Gait training early after stroke with a new exoskeleton--the hybrid assistive limb: a study of safety and feasibility. *Journal of neuroengineering and rehabilitation.* 2014;11:92.

43. Lin LF, Huang SW, Chang KH, Ouyang JH, Liou TH, Lin YN. A novel Robotic Gait Training System (RGTS) may facilitate functional recovery after stroke: A feasibility and safety study. *NeuroRehabilitation.* 2017;41(2):453-461.

44. Lee SY, Han EY, Kim BR, Chun MH, Lee YK. Can Lowering the Guidance Force of Robot-Assisted Gait Training Induce a Sufficient Metabolic Demand in Subacute Dependent Ambulatory Patients With Stroke? *Archives of physical medicine and rehabilitation.* 2017;98(4):695-700.

45. Stoller O, Rosemeyer H, Baur H, et al. Short-time weight-bearing capacity assessment for non-ambulatory patients with subacute stroke: reliability and discriminative power. *BMC Res Notes.* 2015;8:723.

46. Hoyer E, Opheim A, Strand LI, Moe-Nilssen R. Temporal and spatial gait parameters in patients dependent on walking assistance after stroke: reliability and agreement between simple and advanced methods of assessment. *Gait & posture.* 2014;40(1):101-106.

47. Han EY, Im SH, Kim BR, Seo MJ, Kim MO. Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial. *Medicine (Baltimore).* 2016;95(41):e5078.

48. van Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, de Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. *Disability and rehabilitation Assistive technology.* 2015;10(2):141-148.

49. Hesse S, Waldner A, Tomelleri C. Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. *Journal of neuroengineering and rehabilitation.* 2010;7:30.

50. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. *Journal of rehabilitation research and development.* 2000;37(6):701-708.

51. Franceschini M, Carda S, Agosti M, et al. Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke?: a single-blind, randomized, controlled trial. *Stroke.* 2009;40(9):3079-3085.

52. Hesse S, Tomelleri C, Bardeleben A, Werner C, Waldner A. Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients. *Journal of rehabilitation research and development.* 2012;49(4):613-622.

53. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. *Stroke.* 2007;38(2):349-354.

54. Mayr A, Kofler M, Quirbach E, Matzak H, Frohlich K, Saltuari L. Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. *Neurorehabilitation and neural repair.* 2007;21(4):307-314.

55. Plummer P, Behrman AL, Duncan PW, et al. Effects of stroke severity and training duration on locomotor recovery after stroke: a pilot study. *Neurorehabilitation and neural repair.* 2007;21(2):137-151.

56. Teixeira da Cunha Filho I, Lim PA, Qureshy H, Henson H, Monga T, Protas EJ. A comparison of regular rehabilitation and regular rehabilitation with supported treadmill ambulation training for acute stroke patients. *Journal of rehabilitation research and development.* 2001;38(2):245-255.

57. Vidoni ED, Tull A, Kluding P. Use of three gait-training strategies in an individual with multiple, chronic strokes. *Journal of neurologic physical therapy : JNPT.* 2008;32(2):88-96.

58. Yagura H, Hatakenaka M, Miyai I. Does therapeutic facilitation add to locomotor outcome of body weight--supported treadmill training in nonambulatory patients with stroke? A randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2006;87(4):529-535.

59. Richards CL, Malouin F, Wood-Dauphinee S, Williams JI, Bouchard JP, Brunet D. Task-specific physical therapy for optimization of gait recovery in acute stroke patients. *Archives of physical medicine and rehabilitation.* 1993;74(6):612-620.

60. Mehrholz J, Werner C, Hesse S, Pohl M. Immediate and long-term functional impact of repetitive locomotor training as an adjunct to conventional physiotherapy for non-ambulatory patients after stroke. *Disability and rehabilitation.* 2008;30(11):830-836.

61. Ochi M, Wada F, Saeki S, Hachisuka K. Gait training in subacute non-ambulatory stroke patients using a full weight-bearing gait-assistance robot: A prospective, randomized, open, blinded-endpoint trial. *J Neurol Sci.* 2015;353(1-2):130-136.

62. Bergmann J, Krewer C, Bauer P, Koenig A, Riener R, Muller F. Virtual reality to augment robot-assisted gait training in non-ambulatory patients with a subacute stroke: a pilot randomized controlled trial. *European journal of physical and rehabilitation medicine.* 2018;54(3):397-407.

63. Ada L, Dean CM, Vargas J, Ennis S. Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review. *Journal of physiotherapy.* 2010;56(3):153-161.

64. Seki K, Sato M, Handa Y. Increase of muscle activities in hemiplegic lower extremity during driving a cycling wheelchair. *The Tohoku journal of experimental medicine.* 2009;219(2):129-138.

65. Sugita N, Yoshizawa M, Kojima Y, et al. Evaluation of motor performances of hemiplegic patients using a virtual cycling wheelchair: an exploratory trial. *Comput Math Methods Med.* 2013;2013:512965.

66. Wang Z, Wang L, Fan H, et al. Adapted low intensity ergometer aerobic training for early and severely impaired stroke survivors: a pilot randomized controlled trial to explore its feasibility and efficacy. *Journal of physical therapy science.* 2014;26(9):1449-1454.

67. da Cunha IT, Jr., Lim PA, Qureshy H, Henson H, Monga T, Protas EJ. Gait outcomes after acute stroke rehabilitation with supported treadmill ambulation training: a randomized controlled pilot study. *Archives of physical medicine and rehabilitation.* 2002;83(9):1258-1265.

68. Kollen B, Kwakkel G, Lindeman E. Longitudinal robustness of variables predicting independent gait following severe middle cerebral artery stroke: a prospective cohort study. *Clinical rehabilitation.* 2006;20(3):262-268.

69. Nozoe M, Kanai M, Kubo H, Kitamura Y, Shimada S, Mase K. Changes in quadriceps muscle thickness in acute non-ambulatory stroke survivors. *Topics in stroke rehabilitation.* 2016;23(1):8-14.

70. Stoller O, de Bruin ED, Schuster-Amft C, Schindelholz M, de Bie RA, Hunt KJ. Cardiovascular rehabilitation soon after stroke using feedback-controlled robotics-assisted treadmill exercise: study protocol of a randomised controlled pilot trial. *Trials.* 2013;14:304.

71. Uhlenbrock D, Sarkodie-Gyan T, Reiter F, Konrad M, Hesse S. [Development of a gait trainer with regulated servo-drive for rehabilitation of locomotor disabled patients]. *Biomed Tech (Berl).* 1997;42(7-8):196-202.

72. Mehrholz J, Rutte K, Pohl M. Jump training is feasible for nearly ambulatory patients after stroke. *Clinical rehabilitation.* 2006;20(5):406-412.

73. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *The Cochrane database of systematic reviews.* 2016;3:CD003316.

74. D'Isabella NT, Shkredova DA, Richardson JA, Tang A. Effects of exercise on cardiovascular risk factors following stroke or transient ischemic attack: a systematic review and meta-analysis. *Clinical rehabilitation.* 2017:269215517709051.

75. Ivey FM, Hafer-Macko CE, Macko RF. Exercise training for cardiometabolic adaptation after stroke. *J Cardiopulm Rehabil Prev.* 2008;28(1):2-11.

76. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: A mixed-methods systematic review and meta-analysis. *Brain Behav.* 2018;8(7):e01000.

77. Kohok DD, Sico JJ, Baye F, et al. Post-stroke hypertension control and receipt of health care services among veterans. *J Clin Hypertens.* 2018;20(2):382-387.

78. Dennis M, Sandercock P, Graham C, Forbes J, Smith J. The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial: a randomised controlled trial to determine whether or not intermittent pneumatic compression reduces the risk of post-stroke deep vein thrombosis and to estimate its cost-effectiveness. *Health technology assessment (Winchester, England).* 2015;19(76):1-90.

79. Lennon O, Blake C. Cardiac rehabilitation adapted to transient ischaemic attack and stroke (CRAFTS): a randomised controlled trial. *BMC neurology.* 2009;9:9.

80. O'Donovan G, Hamer M. The association between leisure-time physical activity and lung function in older adults: The English longitudinal study of ageing. *Preventive medicine.* 2018;106:145-149.

81. Ezeugwu VE, Olaogun M, Mbada CE, Adedoyin R. Comparative lung function performance of stroke survivors and age-matched and sex-matched controls. *Physiother Res Int.* 2013;18(4):212-219.

82. Vingerhoets F, Bogousslavsky J. Respiratory dysfunction in stroke. *Clin Chest Med.* 1994;15(4):729-737.

83. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. *Stroke research and treatment.* 2012;2012:959120.

84. de Almeida IC, Clementino AC, Rocha EH, Brandao DC, Dornelas de Andrade A. Effects of hemiplegy on pulmonary function and diaphragmatic dome displacement. *Respiratory physiology & neurobiology.* 2011;178(2):196-201.

85. Sisante JF, Mattlage AE, Arena R, Rippee MA, Billinger SA. Decreased tidal volume may limit cardiopulmonary performance during exercise in subacute stroke. *J Cardiopulm Rehabil Prev.* 2015;35(5):334-341.

86. van der Palen J, Rea TD, Manolio TA, et al. Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax.* 2004;59(12):1063-1067.

87. Jang SH, Bang HS. Effect of thoracic and cervical joint mobilization on pulmonary function in stroke patients. *Journal of physical therapy science.* 2016;28(1):257-260.

88. Kim J, Park JH, Yim J. Effects of respiratory muscle and endurance training using an individualized training device on the pulmonary function and exercise capacity in stroke patients. *Medical science monitor : international medical journal of experimental and clinical research.* 2014;20:2543-2549.

89. Huo K, Hashim SI, Yong KL, Su H, Qu QM. Impact and risk factors of post-stroke bone fracture. *World J Exp Med.* 2016;6(1):1-8.

90. Pang MY, Eng JJ, McKay HA, Dawson AS. Reduced hip bone mineral density is related to physical fitness and leg lean mass in ambulatory individuals with chronic stroke. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2005;16(12):1769-1779.

91. Tomasevic-Todorovic S, Simic-Panic D, Knezevic A, Demesi-Drljan C, Maric D, Hanna F. Osteoporosis in patients with stroke: A cross-sectional study. *Ann Indian Acad Neurol.* 2016;19(2):286-288.

92. Pang MY, Yang FZ, Jones AY. Vascular elasticity and grip strength are associated with bone health of the hemiparetic radius in people with chronic stroke: implications for rehabilitation. *Physical therapy.* 2013;93(6):774-785.

93. Pang MY, Yang FZ, Lau RW, Cheng AQ, Li LS, Zhang M. Changes in bone density and geometry of the upper extremities after stroke: a case report. *Physiotherapy Canada Physiotherapie Canada.* 2012;64(1):88-97.

94. Borschmann K, Pang MY, Bernhardt J, Iuliano-Burns S. Stepping towards prevention of bone loss after stroke: a systematic review of the skeletal effects of physical activity after stroke. *International journal of stroke : official journal of the International Stroke Society.* 2012;7(4):330-335.

95. Chung ME, Lee JI, Im S, Park JH. Ischemic stroke in rats enhances bone resorption in vitro. *J Korean Med Sci.* 2012;27(1):84-88.

96. Borschmann KN, Rewell SS, Iuliano S, et al. Reduced bone formation markers, and altered trabecular and cortical bone mineral densities of non-paretic femurs observed in rats with ischemic stroke: A randomized controlled pilot study. *PLoS One.* 2017;12(3):e0172889.

97. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation.* 2014;45(8):2532-2553.

98. Winstein CJ, Stein J, Arena R, et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016;47(6):e98-e169.

99. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke.* 2007;38(10):2752-2758.

100. Dennis M, Mordi N, Graham C, Sandercock P. The timing, extent, progression and regression of deep vein thrombosis in immobile stroke patients: observational data from the CLOTS multicenter randomized trials. *J Thromb Haemost.* 2011;9(11):2193-2200.

101. Ivey FM, Womack CJ, Kulaputana O, Dobrovolny CL, Wiley LA, Macko RF. A single bout of walking exercise enhances endogenous fibrinolysis in stroke patients. *Medicine and science in sports and exercise.* 2003;35(2):193-198.

102. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Stroke.* 2004;35(5):1230-1240.

103. Jones AY, Kam C, Lai KW, et al. Changes in heart rate and R-wave amplitude with posture. *The Chinese journal of physiology.* 2003;46(2):63-69.

104. MacKay-Lyons MJ, Makrides L. Cardiovascular stress during a contemporary stroke rehabilitation program: is the intensity adequate to induce a training effect? *Archives of physical medicine and rehabilitation.* 2002;83(10):1378-1383.

105. Young DR, Hivert MF, Alhassan S, et al. Sedentary Behavior and Cardiovascular Morbidity and Mortality: A Science Advisory From the American Heart Association. *Circulation.* 2016.

106. Bakkum AJ, de Groot S, Stolwijk-Swuste JM, et al. Effects of hybrid cycling versus handcycling on wheelchair-specific fitness and physical activity in people with long-term spinal cord injury: a 16-week randomized controlled trial. *Spinal Cord.* 2015;53(5):395-401.

107. Mackay-Lyons M, McDonald A, Matheson J, Eskes G, Klus MA. Dual effects of body-weight supported treadmill training on cardiovascular fitness and walking ability early after stroke: a randomized controlled trial. *Neurorehabilitation and neural repair.* 2013;27(7):644-653.

108. Stoller O, Schindelholz M, Bichsel L, et al. Feedback-controlled robotics-assisted treadmill exercise to assess and influence aerobic capacity early after stroke: a proof-of-concept study. *Disability and rehabilitation Assistive technology.* 2014;9(4):271-278.

109. Maguire CC, Sieben JM, de Bie RA. The influence of walking-aids on the plasticity of spinal interneuronal networks, central-pattern-generators and the recovery of gait post-stroke. A literature review and scholarly discussion. *J Bodyw Mov Ther.* 2017;21(2):422-434.

110. Coplan NL, Gleim GW, Scandura M, Nicholas JA. Comparison of arm and treadmill exercise at 85% predicted maximum heart rate. *Clinical cardiology.* 1987;10(11):655-657.

111. Goldraich L, Ross HJ, Foroutan F, Walker M, Braga J, McDonald MA. Reevaluating Modality of Cardiopulmonary Exercise Testing in Patients with Heart Failure and Resynchronization Therapy: Relevance of Heart Rate-Adaptive Pacing. *J Card Fail.* 2017;23(5):422-426.

112. Jack LP, Purcell M, Allan DB, Hunt KJ. Comparison of peak cardiopulmonary performance parameters during robotics-assisted treadmill exercise and arm crank ergometry in incomplete spinal cord injury. *Technol Health Care.* 2010;18(4-5):285-296.

113. Katz-Leurer M, Shochina M, Carmeli E, Friedlander Y. The influence of early aerobic training on the functional capacity in patients with cerebrovascular accident at the subacute stage. *Archives of physical medicine and rehabilitation.* 2003;84(11):1609-1614.

114. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology.* 2012;2(2):1143-1211.

115. Winter DA, MacKinnon CD, Ruder GK, Wieman C. An integrated EMG/biomechanical model of upper body balance and posture during human gait. *Progress in brain research.* 1993;97:359-367.

116. Veerbeek JM, Koolstra M, Ket JC, van Wegen EE, Kwakkel G. Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis. *Stroke.* 2011;42(11):3311-3315.

117. Belda-Lois JM, Mena-del Horno S, Bermejo-Bosch I, et al. Rehabilitation of gait after stroke: a review towards a top-down approach. *Journal of neuroengineering and rehabilitation.* 2011;8:66.

118. Arya KN, Pandian S. Interlimb neural coupling: implications for poststroke hemiparesis. *Annals of physical and rehabilitation medicine.* 2014;57(9-10):696-713.

119. Mehrholz J, Pohl M, Elsner B. Treadmill training and body weight support for walking after stroke. *The Cochrane database of systematic reviews.* 2014;1:CD002840.

120. Franceschini M, Carda S, Agosti M, Antenucci R, Malgrati D, Cisari C. Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke?: a single-blind, randomized, controlled trial. *Stroke.* 2009;40(9):3079-3085.

121. Pang MY, Eng JJ, Dawson AS, McKay HA, Harris JE. A community-based fitness and mobility exercise program for older adults with chronic stroke: a randomized, controlled trial. *J Am Geriatr Soc.* 2005;53(10):1667-1674.

122. Pang MY, Ashe MC, Eng JJ, McKay HA, Dawson AS. A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2006;17(11):1615-1625.

123. Rector RS, Rogers R, Ruebel M, Hinton PS. Participation in road cycling vs running is associated with lower bone mineral density in men. *Metabolism: clinical and experimental.* 2008;57(2):226-232.

124. Rector RS, Rogers R, Ruebel M, Widzer MO, Hinton PS. Lean body mass and weight-bearing activity in the prediction of bone mineral density in physically active men. *J Strength Cond Res.* 2009;23(2):427-435.

125. Mobarake BG, Banitalebi E, Ebrahimi A, Ghafari M. Effect of Progressive Locomotor Treadmill Compared to Conventional Training on Bone Mineral Density and Bone Remodeling in Paraplegia. *Middle East Journal of Rehabilitation and Health.* 2017;4(1).

126. Carvalho DC, Garlipp CR, Bottini PV, Afaz SH, Moda MA, Cliquet A, Jr. Effect of treadmill gait on bone markers and bone mineral density of quadriplegic subjects. *Braz J Med Biol Res.* 2006;39(10):1357-1363.

127. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise.* 2011;43(7):1334-1359.

128. Gupta N, Heiden M, Aadahl M, Korshoj M, Jorgensen MB, Holtermann A. What Is the Effect on Obesity Indicators from Replacing Prolonged Sedentary Time with Brief Sedentary Bouts, Standing and Different Types of Physical Activity during Working Days? A Cross-Sectional Accelerometer-Based Study among Blue-Collar Workers. *PLoS One.* 2016;11(5):e0154935.

129. Thorp AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. *Medicine and science in sports and exercise.* 2014;46(11):2053-2061.

130. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes care.* 2008;31(4):661-666.

131. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev.* 2010;38(3):105-113.

132. Dempsey PC, Sacre JW, Larsen RN, et al. Interrupting prolonged sitting with brief bouts of light walking or simple resistance activities reduces resting blood pressure and plasma noradrenaline in type 2 diabetes. *Journal of hypertension.* 2016;34(12):2376-2382.

133. Pronk NP, Katz AS, Lowry M, Payfer JR. Reducing occupational sitting time and improving worker health: the Take-a-Stand Project, 2011. *Prev Chronic Dis.* 2012;9:E154.

134. Alzahrani MA, Dean CM, Ada L, Dorsch S, Canning CG. Mood and Balance are Associated with Free-Living Physical Activity of People after Stroke Residing in the community. *Stroke research and treatment.* 2012;2012:470648.

135. Smith PS, Thompson M. Treadmill training post stroke: are there any secondary benefits? A pilot study. *Clinical rehabilitation.* 2008;22(10-11):997-1002.

136. Yang CY, Tsai JC, Huang YC, Lin CC. Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. *J Adv Nurs.* 2011;67(1):158-168.

137. Mitchell AJ, Sheth B, Gill J, et al. Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. *Gen Hosp Psychiatry.* 2017;47:48-60.

138. Srivastava A, Taly AB, Gupta A, Murali T. Post-stroke depression: prevalence and relationship with disability in chronic stroke survivors. *Ann Indian Acad Neurol.* 2010;13(2):123-127.

139. Jeong YJ, Kim WC, Kim YS, Choi KW, Son SY, Jeong YG. The Relationship between Rehabilitation and Changes in Depression in Stroke Patients. *Journal of physical therapy science.* 2014;26(8):1263-1266.

140. Morone G, Bragoni M, Iosa M, et al. Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. *Neurorehabilitation and neural repair.* 2011;25(7):636-644.

141. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2006;87(10):1298-1304.

Chapter 3: Feasibility of aerobic walking exercise and the trend of pulmonary function change in non-ambulatory stroke survivors, a pilot trial

Abstract

Background: Lung function is compromised in stroke survivors, which may cause fatigue and exercise intolerance. Furthermore, past studies of aerobic exercise have involved only stroke survivors who could walk independently. Stroke survivors who were unable to walk were not included in previous research investigating changes in lung function from walking exercise interventions. In this pilot study, the feasibility and the effect of aerobic walking exercise on lung function was examined in non-ambulatory stroke survivors using a treadmill, body weight support system, and a gait training device.

Methods: 9 non-ambulatory stroke survivors (5 males, mean age 61.8 ± 13.6 years, 8 with ischemic stroke) completed a low intensity walking exercise program (30 minutes/session; three sessions/week for eight weeks), and 8 of them completed the lung function test. Before and after the intervention, vital capacity (VC) and forced vital capacity (FVC) using a spirometer were measured according to the guideline from American Thoracic Society/European Respiratory Society.

Results: The rates of compliance were 100% in the nine participants who completed the intervention, and the attrition rate was 10%. No adverse events were reported. There were significant differences between pre- and post -intervention assessments in FVC ($p= 0.09$), percentage of predicted VC ($p= 0.08$), and percentage of predicted FVC ($p= 0.08$).

Conclusions: The specific aerobic walking exercise used in the current study is feasible and safe in non-ambulatory stroke survivors. The results show a trend of improvement in pulmonary function after the aerobic walking exercise, even though more clinical trial studies are needed.

Keywords

Non-ambulatory; stroke; lung; spirometer; walking

Introduction

Stroke affects the brain hemispheres following a rupture or blocking of one or multiple cerebrovascular arteries,[1] and often leads to hemiplegia in the contralateral side of human body.[1] In addition to neurologic deficits, during their recovery stroke survivors often have a significant complaint of fatigue and reduced endurance for activities.[2] Due to weakness in trunk and respiratory muscles in the affected side, stroke survivors usually show compromised trunk performance and impaired lung function.[3-5] Diminished trunk performance and impairment in lung function can significantly hinder performance in daily activities and increase the risk of cardiovascular disease.[6] In addition, impairments in lung function predispose stroke survivors to rapid fatigue and exercise intolerance, which significantly limit their functional activities of daily living and their participation in rehabilitaiton programs.[7] Reduced lung function in stroke survivors increases the risk of recurrence of stroke and risk of pulmonary infection due to an inability to clear their lungs efficiently from mucus. [8-10] Physical inactivity can also lead to impaired respiratory function over time in chronic stroke survivors.[11]

Significant benefits of physical exercise on pulmonary function have been supported by evidence from past clinical studies of stroke survivors with mild and moderate disability, but none of these studies have targeted non-ambulatory stroke survivors. The reported benefits of exercise include improvement in the maximum oxygen consumption,[12-17] walking distance and velocity,[13,14,16,17] workload,[12] and tolerance to exercise.[12] These past studies did not involve severely disabled, non-ambulatory stroke survivors. However, some indirect evidence indicates potential benefits of walking exercise on pulmonary function in severely disabled, non-ambulatory people. For instance, walking on treadmill with body weight support system for four weeks improved lung function in severely disabled people after spinal cord injury.[18] Trunk muscles including respiratory muscle are stimulated during standing and walking to maintain balance;[19] and therefore, walking exercise can strengthen weakened respiratory muscles. Non-ambulatory stroke survivors have a compromised trunk performance secondary to trunk and respiratory muscles weakness in the affected side,[3,4] and their lung function is impaired and at higher risk of lung infection diseases.[4,20] Since stroke is a neurological disorder, stroke survivors might suffer a restrictive lung abnormality due to respratory muscles weakness.[21] Thus, we conducted this study to investigate the effect of eight weeks of aerobic walking exercise on lung function in non-ambulatory stroke survivors, in terms of vital capacity (VC), which is the maximum air that can be exhaled slowly until the lung is felt empty of air,[21] and forced vital capacity (FVC), which is the volume of air that can be forcibly and fully expired following a full inhalation.[21] The risk of heart diseases and recurrent stroke are higher in stroke survivors when they have a reduced FVC.[10] Improvement in VC and FVC might be an indicator of improvement in respiratory muscles strength.[21] To our knowledge, no studies have examined the effect of aerobic walking exercise on lung function in non-ambulatory stroke survivors who score ≤ 2 on the functional ambulation category (FAC), which is a functional test that evaluates the walking ability.[22]

The primary aim of this pilot study was to examine the feasibility of an aerobic walking exercise program using a treadmill, body weight support system, and an assistive walking device, including measures of recruiting procedure (number of participants screened, number of participants qualified, and number of participants enrolled), compliance rate and dropout rate among study participants. In addition, we assessed the participants' acceptance regarding our intervention and the use of our assistive walking device. The secondary aim of the study was to investigate the effect of aerobic walking exercise on lung function in non-ambulatory stroke survivors. We hypothesized that VC and FVC will be significantly improved in non-ambulatory stroke survivors after eight weeks of aerobic walking exercise.

Materials and methods

Study design

This pilot feasibility study enrolled a single group (n=10) of non-ambulatory stroke survivors participating in an aerobic walking exercise program (three sessions/week for eight weeks) and evaluated their VC and FVC at baseline and post-intervention. All walking exercise and evaluation sessions were conducted in the Neuromuscular Research Laboratory at the University of Kansas Medical Center (KUMC). The study participants were stroke survivors with their first stroke who met our inclusion criteria: being between 18 and 80 years of age, unable to walk independently according to FAC (≤ 2), having a stroke 0.5 to 5 years ago, walking independently before stroke, being able to complete spirometer testing, being able to follow directions in English, and being able to attend all of the intervention sessions. Stroke survivors were excluded who had previous pulmonary diseases, unstable medical conditions, and musculoskeletal disorders which might prevent the participant from performing walking exercise. Study participants were stroke survivors at least 6 months post stroke in order to make sure that their non-ambulation status was confirmed after trials of rehabilitation treatments within the first 6 months after stroke. Study participants were primarily recruited from the Physical Medicine and Rehabilitation clinic at the University of Kansas (KU) Hospital. In addition, exercise facilities of the American Stroke Foundation in the greater Kansas City metropolitan area were used to recruit study participants. The Healthcare Enterprise Repository for Ontological Narration (HERON), a database managed at KUMC, was used to obtain information about stroke patients who were admitted to KU Hospital after acute stroke and agreed to be contacted for opportunities to participate in research projects. We also placed our study flyers in local rehabilitation clinics offices. Before starting the intervention, each participant received the detailed information about the study and signed an informed consent approved by the KUMC institutional review board (IRB).

Measurements

To measure the feasibility, number of participants who were screened, qualified, excluded, enrolled, and completed the intervention were recorded. The participants were contacted via phone, email, or in-person meeting. In addition, an end intervention questionnaire (table 2) was given to the participants to assess their acceptance regarding our intervention and the assistive walking device, and it was collected at the post-intervention session. The end intervention questionnaire (table 2) contains 12 statements, and each statement has five levels of choices. The end intervention questionnaire has two sections; the first section has seven statements regarding the walking training program, and the second section has five statements regarding the assistive walking training device (figure 1).

Lung function outcome measurements were conducted at baseline assessment session and post-intervention assessment session which occurred within one week after last intervention session. Arm span was utilized to estimate the height of our participants because all participants were not able to stand up straight.[23] Body weight was measured through two force plates while participant sitting on a wheelchair. The same wheelchair was used in body weight measurement for all participants to ensure the consistence on body weight measurement. We utilized the arm span and weight to obtain participant's body mass index. Vital capacity (VC) and forced vital capacity (FVC) of the participants were measured using a hand-held spirometer (MIR Spirotel Spirometer, New Berlin, WI, USA), following the guidelines by the American Thoracic Society/European Respiratory Society.[24] In brief, a nose clip was used, and participants were instructed to seal their lips around the mouthpiece to prevent air leaking. To measure VC, the participant was in a sitting position and breathed normally three times first, and then was instructed to slowly and maximally inhale and immediately slowly and maximally exhale. The subjects were instructed to completely fill and empty their lungs during maximal inhalation and exhalation. In this manner, it was repeated four times or until three acceptable readings were obtained with less than 0.15 L differences between readings. To measure FVC, the subjects were instructed to forcibly maximally inhale. Immediately, they were instructed to exhale forcibly and maximally. This test was repeated a minimum of three times. The differences between readings should not be greater than 0.150 L. If the differences exceeded 0.150 L, the test would be repeated a maximum of eight times or until we obtained three acceptable readings. Percentages of predicted VC (% of Pred. VC) and FVC (% of Pred. FVC) were calculated by the spirometer's application, and they were calculated depending on age, gender, and body mass index. Participants rested for at least one minute between each repetition to avoid fatigue. These tests would be stopped if any adverse event happen, such as dizziness, and we would wait for a while until it subsided before repeating the test again. Lung function test would not be conducted if the stroke survivor had a facial palsy or restricted movement of the lips. In addition, participant's other physical activities within the intervention duration were recorded weekly by using a physical activity log.

Aerobic walking exercise

During aerobic walking exercise, a participant walked on a treadmill for about 30 minutes, three times per week for eight weeks. A harness was attached to the ceiling and was tightened around participant's waist, thighs and hips to support partial body weight and protect the participant from falling. About 40% of the participant's weight was supported initially at the first training session. The body weight support was gradually reduced over time in late training sessions, if the participant could perform the walking exercise. We utilized an assistive device to help the participant in making steps forward by the affected lower limbs (figure 1). Using this device, a physical therapist was able to provide the affected lower limb with assistance in hip and knee flexion and ankle dorsiflexion during swing phase by pulling a cable.[25] To reach a low intensity exercise, the target heart rate zone was between 30% and 40% of exercise intensity using the heart rate reserve. The equation to calculate the heart rate reserve is [(maximum heart rate – resting heart rate) * % of targeted exercise intensity] + resting heart rate.[26] The maximum heart rate was determined using an age-predicted maximum heart rate (220 – participant's age),[26,27] and we subtracted 10 beats if the participant was on beta blocker medication.[28] The walking exercise started with two minutes of warming up at the speed of 0.6 mile/hour. The treadmill speed was then increased gradually until the heart rate reached the target heart rate zone. We ended a session of walking exercise with two minutes of cooling down. The duration of a walking exercise session was determined individually according to the participant's tolerance. It was initially set at 10 minutes and increased weekly by 5 minutes until we reached the targeted duration of 30 minutes for each session. An optical heart rate sensor (Polar OH1) was placed on participant's non-affected forearm to monitor heart rate continuously during walking exercise. One physical therapist stood behind the participant to control trunk movement and to encourage the participant verbally. Another physical therapist operated the walking assistive device by pulling and releasing a cable to assist every step forward of the affected leg/foot.[25] Blood pressure of the participant was monitored before, at the middle, and at the end of each exercise session to ensure safety. If the participant felt tired, we would pause the walking exercise for two minutes and measured the blood pressure of the participant for safety purposes. At the end of each exercise session we asked the participants to rate the intensity of exercise using the 6 to 20 Borg rating of perceived exertion scale (RPE) scale. On a daily exercise log, we recorded the RPE, treadmill speed, percentage of body weight supported, and duration of the session after each exercise session. Each exercise session throughout the intervention process lasted approximately one hour, ranging from 30 to 60 minutes, including the time for set up.

Statistical Analysis

Descriptive statistics were used to summarize means, standard deviations, and confidence intervals for outcome measures. Paired t-test as well as Wilcoxon signed rank test was used to analyze within-group difference of pre- and post-intervention results of lung function measurements and RPE using SPSS software (IBM SPSS statistics version 25). The significance level was set at 0.1 because of a limited sample size.[29]

Results

Participants' characteristics

Ten non-ambulatory stroke survivors were recruited, and eight of them completed lung function data. One participant withdrew from the study due to family issues. One other participant could not perform the lung function test due to facial muscles weakness. The remaining eight participants completed the study and lung function test. They were five men and four women with a mean age of 61.8 ± 13.6 years. Their onset of stoke incidence ranged from 7 to 52 months prior to the participation of this study. Table 1 shows the participants' demographic and anthropometric data for nine participants.

Feasibility measurements

Study flowchart in (figure 2) shows number of participants who were screened, qualified, excluded, enrolled, and completed the intervention. Initially, 247 stroke survivors were screened for eligibility through their phones and emails or met in person by a study team member. Ten individuals who qualified for our study were enrolled. One participant completed four weeks of walking exercise intervention and dropped out due to family reasons (10% drop out rate). Nine participants completed the intervention with 100% compliance rate for all walking exercise sessions. The most two barriers for non-ambulatory stroke survivors to participate in our intervention were lacking transportation and living far away from our lab. No adverse events were recorded during the intervention.

Nine participants provided answers to the end-intervention questions after the completion of walking exercise intervention (table 2). In their response to questions regarding the walking exercise program, the choice of Strongly Agree or Agree was selected by 8 (satisfied with time length and procedures), 9 (safe and secure), 8 (comfortable), 9 (enjoyed), 9 (participate again), 7 (improves life), and 6 (improved walking ability), respectively. In their responses to questions regarding the assistive walking device, the choice of Strongly Agree was selected by 9 (safe and secure), 9 (comfortable), 9 (provided sufficient assistance), 8 (setting up was reasonable), and 9 (recommend using this assistive device by others), respectively.

Changes in pulmonary function

There were significant differences between pre- and post -intervention assessments in FVC, % of predicted VC, and % of predicted FVC (table 3). The FVC increased significantly from 2.26±1.0 L to 2.37±0.89 L ($p<0.1$, effect size = 0.53). The % of predicted VC increased significantly from 62.25±23.42% to 65.5±20.89% ($p<0.1$, effect size = 0.55). The % of predicted FVC increased significantly from 58.5±21.9% to 61.88±20.84% ($p<0.1$, effect size = 0.58). The VC increased from 2.41±0.87 L to 2.53±0.77 L, but not statistically significant ($p=0.14$, effect size = 0.41). The means of pre- and post-intervention of RPE decreased from 13.75±3.31 to 12.37±3.62, but the difference was not statistically significant ($p= 0.4$). The results were similar when we utilized Wilcoxon signed rank test (nonparametric) and paired t-test (parametric).

Discussion

Ten non-ambulatory stroke survivors were enrolled into this study, and nine of them completed eight weeks of low intensity aerobic walking exercise. The attrition rate was 10%. In recruiting study participants, we contacted 247 stroke survivors in-person or through phone calls or emails (figure 2). The majority of the contacted individuals did not qualify for the study due to being able to walk (n=183) and living far away (n=32). Among 32 individuals who qualified for the study, 18 had difficulty in obtaining transportation for participating in the study; 4 declined to participate in the study; and 10 were enrolled in the study. The enrollment rate (31%) from qualified potential subjects may be improved in future study if transportation can be provided to participants. Most of our participants in this study presented high acceptance for the walking exercise program and the assistive training device in their response to the end-intervention questionnaire. No adverse events occurred during the intervention indicating the safety of low intensity walking exercise for non-ambulatory stroke survivors.

Our results indicate a promise that the aerobic walking exercise may help people who are non-ambulatory after stroke. Significant improvements were observed in three out of four outcome measurements of pulmonary function. The change in VC measurement showed a trend towards significant improvement, even though not statistically significant. Our results cannot be directly compared to other past studies because this is the first study to investigate the effect of walking exercise on pulmonary function in non-ambulatory chronic stroke survivors. Some indirect comparison of our results with that of studies of walking training on pulmonary function in non-ambulatory patients with spinal cord injury may offer interesting insight. Tiftik et al.[18] conducted walking trining in patients with spinal cord injury with 3 sessions per week for four weeks using a body weight support system and reported significant increases pre- and post-intervention in means of VC by 0.2 L and FVC by 0.1 L, respectively. This result is similar to our results in terms of averaged changes in VC (0.12 L) and FVC (0.11 L). Terson de Paleville et al.[30] conducted 62 sessions (5 sessions/week) of locomotor training using a body weight support system in people with spinal cord injury and reported significant changes in mean of the % of predicted FVC by 7.9%. It is possible that the longer duration and higher frequency of walking exercise in the study by Terson de Paleville et al.[30] might be a partial reason for a larger improvement in the % of predicted FVC compared to our result (3.8%).

We also compared our results with the results of two past studies that examined the changes in pulmonary function after aerobic exercise in stroke survivors with mild or moderate disability. In a pilot study Bang et al.[31] investigated the changes in lung function in chronic ambulatory stroke survivors using a 4-week (5 sessions/week) aerobic cycling exercise at intensity of 50 to 80% of maximum heart rate which was equivalent to 11 to 14 on RPE, and reported that FVC increased significantly by a mean change of 0.5 L. The exercise intensity in the study by Bang et al.[31] (50 to 80% of maximum heart rate) was higher than that in our study (30 to 40% of heart rate reserve) and might partially contribute to the better results in FVC measurement. The side of hemiplegia might be another factor for difference in FVC outcomes. The half of participants in the study by Bang et al.[31] had left side hemiplegia, while all of our participants except one had right sides hemiplegia. Past studies have reported that stroke survivors with right side hemiplegia would have worse impairments in lung function and respiratory muscles when compared to stroke survivors with left side hemiplegia.[32] In another study, Sutbeyaz et al.[23] divided people with mild to moderate stroke into three groups: inspiratory muscles training group, breathing exercise group, and control group. The 6-week daily intervention generated significant improvement only in respiratory muscle training group by 0.13 L in the mean of VC and 0.23 L in the mean of FVC, which is similar to our results. Different levels of disability in participants between our study (severe) and both comparison studies (mild or moderate) may also explain partially the difference in the outcomes of lung function.

An important finding of our study is that the aerobic walking exercise even at a low exercise intensity, i.e. between 30% and 40% of the heart rate reserve, was able to generate significant improvement in lung function in non-ambulatory stroke survivors. Moderate to high exercise intensity (40 % to 70% of heart rate reserve) is recommended to improve physical health in stroke survivors with mild or moderate impairment.[33] However, there has been a lack of exercise guidelines for non-ambulatory stroke survivors.[33,34] We chose the low exercise intensity in the current study based on the consideration of safety and tolerance of non-ambulatory stroke survivors. In fact, the level of perceived exertion (RPE) recorded from our participants pre- and post-intervention were on average 13.75 and 12.37, which is close to the recorded value of RPE (11 to 14) in the study by Bang et al., in which the exercise intensity was high (50 to 80% of maximum heart rate).[31] It suggested that our participants were at the top level of their physical capacity and tolerance. Past studies suggested that the intensity of physical activity in most of the rehabilitation programs for severely impaired stroke survivors were not enough to enhance pulmonary functions.[10,35] A past study reported that severely impaired stroke survivors could not reach the recommended exercise intensity to induce aerobic effects in a walking exercise using a body weight support system and an automated assistive device.[36] The assistive walking device used in our study was unique in that it provided minimal assistance to the trained stroke survivors and encouraged their active engagement in training activities.[25] This factor may be important for the observed benefit in lung function in our study using a low exercise intensity.

The reasons for the significant improvement in FVC, % of predicted VC, and % of predicted FVC observed in our study might be the increased activities of respiratory muscles and increased strength of trunk muscles after walking exercise.[18,19] Future studies may directly measure the changes in respiratory muscles activity and strength of trunk muscles after the walking exercise using electromyography or maximal inspiratory pressure and maximal expiratory pressure.

There are several limitations in our study. First, no control group and small sample size limit the results to be inconclusive about the effect of our intervention. Furthermore, this study only recruited non-ambulatory stroke survivors at the chronic phase after stroke. Therefore, results from this study should be interpreted with caution and should not be generalized to other conditions. We did not control for the stroke lesion location even though it could significantly affect the lung function. In addition, we did not investigate the long term effect of our intervention. In our intervention, we utilized body weight support system which included a harness. The tightness of harness might affect oxygen consumption, lung capacity, and heart rate negatively,[37,38] which might limit the improvement in vital capacity in our participants.

Conclusion

Our results show that eight weeks of low intensity aerobic walking exercise is feasible and safe for non-ambulatory stroke survivors. In addition, results of our study indicate a potential of the walking exercise in improving pulmonary function in non-ambulatory stroke survivors. Future randomized control trials should be conducted with a larger sample size to investigate the walking training with different intensities on pulmonary function in non-ambulatory stroke survivors.

Table 1: Baseline Participant Demographics for nine participants.

Age (years), mean ± SD, (range: min - max)	61.8 ± 13.6 (40 – 78)
Men/women	5/4
Stroke type: Ischemic/hemorrhagic	8/1
Hemiparetic side: Left/right	1/8
Time since stroke (months)	28.2 ± 14.8 (7 – 52)
Race: White/African-American/other	5/3/1
Body mass index (kg/m^2), mean ± SD, (range: min - max):	28.6 ± 8.2 (15.7 – 42.8)
Smoker: Yes/no	1/8

SD: standard deviation, min: minimum, max: maximum, kg/m^2: kilogram per square meter.

Table 2: The end intervention questionnaire and rating scores provided by the participants.

		Rating scores				
		1	2	3	4	5
Regarding walking training program	I was satisfied with time length and procedures of walking training	0	0	1	0	8
	I felt that walking training was safe and secure	0	0	0	0	9
	I felt that walking training was comfortable in regard to the harness	1	0	0	3	5
	I enjoyed walking training program	0	0	0	2	7
	I would plan to participate in walking training again	0	0	0	0	9
	I felt that walking training improves my life	0	0	2	2	5
	Walking training improves my walking ability	2	1	0	4	2
Regarding the assistive gait device	I felt that the assistive device was safe and secure	0	0	0	0	9
	I felt that the assistive device was comfortable	0	0	0	4	5
	I felt that the assistive device provided sufficient assistance during walking	0	0	0	1	8
	I felt that time for setting up assistive device was reasonable	0	0	1	1	7
	I would recommend using this assistive device by others	0	0	0	0	9

Rating scores: 1= Strongly disagree; 2 = Disagree; 3 = Natural; 4 = Agree; 5 = Strongly agree

Table 3: Lung function outcomes.

	pre-intervention	Post-intervention	Mean Differences	Effect size	90% confidence interval	p-value
VC (L)	2.41 ± 0.87	2.53 ± 0.77	0.12	0.41	-0.07 , 0.32	0.14
FVC (L)	2.26 ± 1.0	2.37 ± 0.89	0.10	0.53	-0.03 , 0.23	0.09*
% of Pred. VC	62.25 ± 23.42	65.5 ± 20.89	3.25	0.55	-0.70 , 7.20	0.08*
% of Pred. FVC	58.5 ± 21.9	61.88 ± 20.84	3.38	058	-0.55 , 7.30	0.08*

VC: vital capacity, FVC: forced vital capacity, % of Pred. VC: percentage of predicted vital capacity, % of Pred. FVC: percentage of predicted forced vital capacity.
* statistically significant ($p < 0.1$), (one tailed).

Figure 1: The assistive walking device which helps the participants in hip flexion and ankle dorsiflexion during swing phase of gait cycle in the affected lower limb.

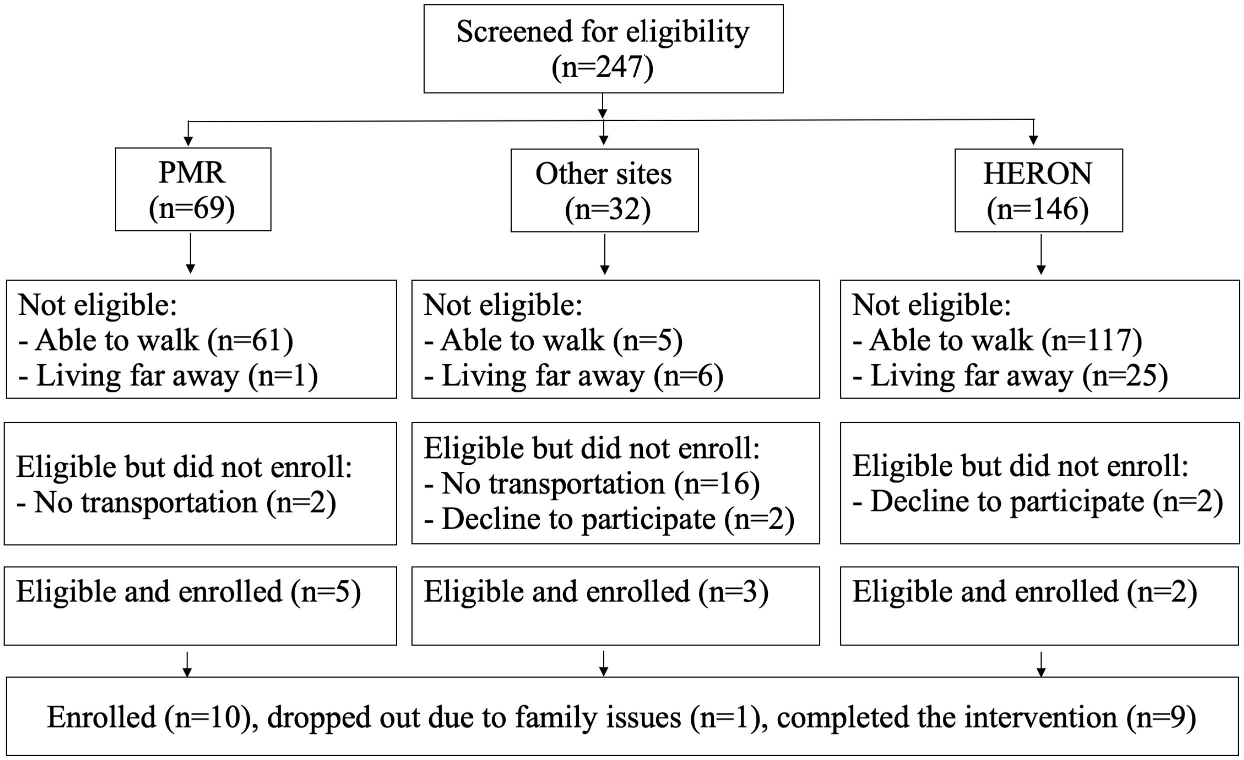

Figure 2: Study flowchart.

PMR: Physical Medicine Rehabilitation clinics at KU hospital, HERON: Healthcare Enterprise Repository for Ontological Narration database hosted at KUMC, Other sites: American Stroke Foundation, and other rehabilitation clinics in the great Kansas City metropolitan area.

References

1. Yew KS, Cheng E. Acute stroke diagnosis. *Am Fam Physician.* 2009;80(1):33-40.
2. Hinkle JL, Becker KJ, Kim JS, et al. Poststroke Fatigue: Emerging Evidence and Approaches to Management: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Stroke.* 2017;48(7):e159-e170.
3. Verheyden G, Vereeck L, Truijen S, et al. Trunk performance after stroke and the relationship with balance, gait and functional ability. *Clinical rehabilitation.* 2006;20(5):451-458.
4. Fugl-Meyer AR, Linderholm H, Wilson AF. Restrictive ventilatory dysfunction in stroke: its relation to locomotor function. *Scand J Rehabil Med Suppl.* 1983;9:118-124.
5. Jandt SR, Caballero RM, Junior LA, Dias AS. Correlation between trunk control, respiratory muscle strength and spirometry in patients with stroke: an observational study. *Physiother Res Int.* 2011;16(4):218-224.
6. Wang Z, Wang L, Fan H, Lu X, Wang T. Effect of low-intensity ergometer aerobic training on glucose tolerance in severely impaired nondiabetic stroke patients. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2014;23(3):e187-193.
7. Ezeugwu VE, Olaogun M, Mbada CE, Adedoyin R. Comparative lung function performance of stroke survivors and age-matched and sex-matched controls. *Physiother Res Int.* 2013;18(4):212-219.
8. van der Palen J, Rea TD, Manolio TA, et al. Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax.* 2004;59(12):1063-1067.
9. Jang SH, Bang HS. Effect of thoracic and cervical joint mobilization on pulmonary function in stroke patients. *Journal of physical therapy science.* 2016;28(1):257-260.
10. Kim J, Park JH, Yim J. Effects of respiratory muscle and endurance training using an individualized training device on the pulmonary function and exercise capacity in stroke patients. *Medical science monitor : international medical journal of experimental and clinical research.* 2014;20:2543-2549.
11. Estenne M, Knoop C, Vanvaerenbergh J, Heilporn A, De Troyer A. The effect of pectoralis muscle training in tetraplegic subjects. *Am Rev Respir Dis.* 1989;139(5):1218-1222.
12. Potempa K, Lopez M, Braun LT, Szidon JP, Fogg L, Tincknell T. Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke.* 1995;26(1):101-105.
13. Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke.* 2005;36(10):2206-2211.

14. Luft AR, Macko RF, Forrester LW, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke.* 2008;39(12):3341-3350.

15. Lennon O, Carey A, Gaffney N, Stephenson J, Blake C. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clinical rehabilitation.* 2008;22(2):125-133.

16. Quaney BM, Boyd LA, McDowd JM, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation and neural repair.* 2009;23(9):879-885.

17. Globas C, Becker C, Cerny J, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabilitation and neural repair.* 2012;26(1):85-95.

18. Tiftik T, Gokkaya NK, Malas FU, et al. Does locomotor training improve pulmonary function in patients with spinal cord injury? *Spinal Cord.* 2015;53(6):467-470.

19. Katz-Leurer M, Shochina M, Carmeli E, Friedlander Y. The influence of early aerobic training on the functional capacity in patients with cerebrovascular accident at the subacute stage. *Archives of physical medicine and rehabilitation.* 2003;84(11):1609-1614.

20. Yuan MZ, Li F, Tian X, et al. Risk factors for lung infection in stroke patients: a meta-analysis of observational studies. *Expert Rev Anti Infect Ther.* 2015;13(10):1289-1298.

21. Dakin J, Mottershaw M, Kourteli E. *Making sense of lung function tests.* CRC Press; 2017.

22. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Physical therapy.* 1986;66(10):1530-1539.

23. Sutbeyaz ST, Koseoglu F, Inan L, Coskun O. Respiratory muscle training improves cardiopulmonary function and exercise tolerance in subjects with subacute stroke: a randomized controlled trial. *Clinical rehabilitation.* 2010;24(3):240-250.

24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.

25. Liu W. A narrative review of gait training after stroke and a proposal for developing a novel gait training device that provides minimal assistance. *Topics in stroke rehabilitation.* 2018;25(5):375-383.

26. Billinger SA, Boyne P, Coughenour E, Dunning K, Mattlage A. Does aerobic exercise and the FITT principle fit into stroke recovery? *Current neurology and neuroscience reports.* 2015;15(2):519.

27. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.

28. Floel A, Werner C, Grittner U, et al. Physical fitness training in Subacute Stroke (PHYS-STROKE)--study protocol for a randomised controlled trial. *Trials.* 2014;15:45.

29. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: A mixed-methods systematic review and meta-analysis. *Brain Behav.* 2018;8(7):e01000.

30. Terson de Paleville D, McKay W, Aslan S, Folz R, Sayenko D, Ovechkin A. Locomotor step training with body weight support improves respiratory motor function in individuals with chronic spinal cord injury. *Respiratory physiology & neurobiology.* 2013;189(3):491-497.

31. Bang DH, Son YL. Effect of intensive aerobic exercise on respiratory capacity and walking ability with chronic stroke patients: a randomized controlled pilot trial. *Journal of physical therapy science.* 2016;28(8):2381-2384.

32. de Almeida IC, Clementino AC, Rocha EH, Brandao DC, Dornelas de Andrade A. Effects of hemiplegy on pulmonary function and diaphragmatic dome displacement. *Respiratory physiology & neurobiology.* 2011;178(2):196-201.

33. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(8):2532-2553.

34. Winstein CJ, Stein J, Arena R, et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016;47(6):e98-e169.

35. Menezes KK, Nascimento LR, Avelino PR, Alvarenga MTM, Teixeira-Salmela LF. Efficacy of Interventions to Improve Respiratory Function After Stroke. *Respiratory care.* 2018;63(7):920-933.

36. van Nunen MP, Gerrits KH, de Haan A, Janssen TW. Exercise intensity of robot-assisted walking versus overground walking in nonambulatory stroke patients. *Journal of rehabilitation research and development.* 2012;49(10):1537-1546.

37. Danielsson A, Sunnerhagen KS. Oxygen consumption during treadmill walking with and without body weight support in patients with hemiparesis after stroke and in healthy subjects. *Archives of physical medicine and rehabilitation.* 2000;81(7):953-957.

38. MacKay-Lyons M, Makrides L, Speth S. Effect of 15% body weight support on exercise capacity of adults without impairments. *Physical therapy.* 2001;81(11):1790-1800.

Chapter 4: Reduction of risk for cardiovascular disease in non-ambulatory stroke survivors using an assisted-walking aerobic exercise: A pilot study

Abstract

Background: Most rehabilitation interventions in stroke rehabilitation are designed with a focus on improving impaired sensorimotor function. While 75% of stroke survivors are prone to having cardiovascular disease, the main cause of death in stroke survivors, fewer efforts have been made on how to control risks of cardiovascular disease after stroke, especially in non-ambulatory stroke survivors.

Objectives: The objectives of this pilot study were to examine the feasibility and trends of a low intensity aerobic walking exercise on cardiovascular risk factors in non-ambulatory stroke survivors using a treadmill, body weight support system, and walking assistive device.

Methods: Nine non-ambulatory stroke survivors (age: 61.8 ± 13.6 years, 5 men, 8 with ischemic stroke) have completed the aerobic walking exercise program (three sessions/week for eight weeks). Glycated hemoglobin (HbA1c), resting heart rate (rHR), systolic (SBP) and diastolic (DBP) blood pressure, and serum level of low-density lipoprotein (LDL) were measured pre- and post-intervention.

Results: Out of 247 stroke survivors, we enrolled 10 stroke survivors who met our inclusion and exclusion criteria. The drop rate was 10% (one participant) due to family reasons, and no adverse events were reported. There were significant changes in HbA1c (from 6.1±0.9 to 5.6±0.7 %), rHR (from 72.6±11.5 to 68.2±12.5 beats/minute), SBP (from 143±14 to 134.1±19 mmHg), and DBP (from 87±11 to 82±7 mmHg) pre- and post-intervention. LDL level did not change significantly (from 103.1±23.1 mg/dl to 101.4±22.8 mg/dl, $p=0.37$).

Conclusion: This pilot study suggests that the aerobic walking exercise is feasible and may improve cardiovascular risk factors in non-ambulatory stroke survivors by decreasing the HbA1c level, rHR, SBP, and DBP.

Key words

Non-ambulatory; stroke; HbA1c; blood pressure; resting heart rate; walking

Introduction

Stroke is a major cause of permanent disability worldwide.[1] Stroke survivors commonly develop cardiovascular dysfunction including cardiac diseases, increased insulin resistance, increased resting heart rate, increased blood pressure, and altered lipids profile. About 75% of stoke survivors suffer from cardiac disease, a prominent cause of death after stroke.[2] More than half of nondiabetic stroke survivors present with insulin resistance during the subacute stage and are prone to diabetes mellitus [3,4] and higher risk of recurrent stroke.[5] Stroke survivors often have an elevated resting heart rate due to prolonged bed rest and sedentary lifestyle, and the elevated resting heart rate is a risk factor for cardiac diseases such as myocardial infarction.[6,7] Blood pressure, a risk factors for recurrent stroke and cardiac disease, is often elevated in more than half of stroke survivors. [8-11] More than 50% of stroke survivors have an impaired lipid profile, which is a risk factor for recurrent stroke.[11] In general, stroke survivors are at high risk of stroke recurrence and/or cardiovascular disease, which may lead to severe disability or death.[3,4,12,13]

Previous studies have reported that pharmacological and non-pharmacological rehabilitation programs may help stroke survivors by improving their motor skills and quality of life.[14-16] The majority of those studies have focused on recovery of sensorimotor function, while only a few studies have focused on cardiovascular health after stroke, particularly in non-ambulatory individuals who are at even higher risk of cardiovascular diseases due to sedentary life style.[17-20,4] In people with mild/moderate disabilities after stroke, aerobic exercise was beneficial in multiple health aspects including cardiovascular health.[21] For non-ambulatory stroke survivors, however, there is limited information about the effect of aerobic exercise on their cardiovascular health.[22-24] So far, only seven studies in the literature have reported cardiovascular outcomes after aerobic exercise in non-ambulatory stroke survivors.[23-29] There were no improvement reported in resting heart rate,[23,25,26,28] peak heart rate,[23,24,26,27,29] resting blood pressure,[25] peak blood pressure,[25-27] or lipid profile [23,24] post-aerobic exercise. One of the limiting factors of these studies could be the short duration of interventions, ranging from 2 to 6 weeks.[23-26,28] More clinical research is required to overcome many limiting factors of past studies and improve outcomes of walking exercise in non-ambulatory stroke survivors.

In this study, we aimed to examine the effect of 8-week aerobic walking exercise using a treadmill, partial body weight supporting system, and a novel assistive walking device on glycemic control, resting heart rate, blood pressure, and lipid profile in non-ambulatory stroke survivors. We hypothesized that our aerobic walking exercise program would significantly decrease glycated hemoglobin (HbA1c), resting heart rate (rHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum level of low-density lipoprotein (LDL), and the score of Patient Health Questionnaire-9 (PHQ-9) in non-ambulatory stroke survivors.

Materials and methods

Study design

This is a single group, pilot, clinical trial designed to investigate the outcomes of eight weeks of aerobic walking exercise in measurements of cardiovascular health including HbA1c, rHR, SBP, DBP, and LDL in non-ambulatory stroke survivors. We defined non-ambulatory stroke survivors as those who cannot walk independently and with a score ≤ 2 on functional ambulation category (FAC).[30] The FAC uses a classification system of six categories. The lowest classification is Category 1 which indicates nonfunctional ambulation and the highest classification is Category 6 which indicates independent ambulation on varying surfaces. We enrolled men and women who suffered from their first stroke at least six months prior to enrollment, between the ages of 18 to 80 years, ambulated independently before the stroke, were able to understand and follow verbal commands in English, were in stable medical condition, and were unable to walk independently according to the FAC (≤ 2) at the beginning of intervention.[30]

We excluded those who had myocardial infarction or coronary artery bypass surgery less than 3 months before recruiting date, unstable angina, renal disease, musculoskeletal disorder which prevents subjects from participating in the exercise, resting blood pressure more than 200/110 mm Hg, and restricted passive movement in the major joints of the lower limbs due to sever spasticity or joint contracture. We also excluded those who were unable to travel to our lab for exercise sessions and those who participated in any walking exercise that aimed to induce aerobic effects using treadmill with or without a body-weight support system. We chose to include chronic stroke survivors because after the first 6 months post stroke and after the rehabilitation treatments have been tried, the condition of non-ambulatory status is determined.

We primarily recruited our study participants from the Physical Medicine and Rehabilitation clinic at the University of Kansas (KU) Hospital. In addition, we visited exercise facilities of American Stroke Foundation at the Greater Kansas City metropolitan area to recruit study participants. We used the Healthcare Enterprise Repository for Ontological Narration (HERON), a database managed at the University of Kansas Medical Center (KUMC), from which we obtained information of stroke patients who were admitted to the KU Hospital after acute stroke and agreed to be contacted for opportunity of participating in research projects. We also placed study flyers in local rehabilitation clinic offices. Before we scheduled the baseline evaluation, a phone screen was used to make sure that the inclusion and exclusion criteria were met. This study was approved by the institutional review board (IRB) at KUMC. All participants provided written informed consent prior to their participation.

Measurements

The primary outcome measurements of the study included HbA1c, rHR, blood pressure, and LDL. In the baseline assessment, the participant came to our research laboratory after fasting for 12 hours. The participants were allowed to rest for 15 minutes in a sitting position, and averages of three readings of rHR and blood pressure of the participant were obtained from brachial artery on nonparetic arm using an automatic blood pressure test device (Microlife blood pressure monitor). About 30 mL of blood was then collected from the antecubital vein in the unaffected arm into a BD Vacutainer serum blood collection tube. Within 30 minutes, after the collected blood clotted, the tube was centrifuged at 2,500 g for 10 minutes at room temperature, to separate serum from cells. Serum was transferred into a clean tube and stored at -80 ºC until analysis. Serum concentration of LDL was determined using the LDL-Cholesterol Human Assay Kit (Crystal Chem, Elk Grove Village, IL, USA; Catalog # 80069). A finger-stick was used to collect a drop of blood sample from the middle finger of the unaffected hand for analysis of the HbA1c level using A1CNow+ System (Test Medical Symptoms at Home, Inc., Maria Stein, OH, USA). The American Diabetes Association and the World Health Organization chose the HbA1c test as a diagnostic tool for diabetes as it indicates a glucose level for eight to 12 weeks.[31] HbA1c has been a reliable test to determine prediabetic and diabetic condition in people with ischemic stroke.[32] The PHQ-9 has nine questions about symptoms of depression within the past two weeks, and each question has a score from 0 (not at all) to 3 (nearly every day). The total PHQ-9 score can range from 0 (no symptoms of depression) to 27 (all symptoms occur every day). Scores $\geq$ 10 indicates major depression. The PHQ-9 is a valid depression screen tool for stroke survivors.[33-35]

Other measurements including body weight, body mass index, percentage of body weight support, Borg rating of perceived exertion scale (RPE), treadmill speed, and walking duration were recorded in each exercise session using an exercise log. All measurements were performed on every participant at baseline and after eight weeks of walking exercise program, and always conducted between 8 and 10 am.

Aerobic walking exercise

During aerobic walking exercise, a participant walked on a treadmill for about 30 minutes, three times per week for eight weeks. A harness was attached to the ceiling and was tightened around participant's waist, thighs and hips to partially support body weight and protect the participant from falling. About 40% of the participant's weight was supported at the first training session. The body weight support was gradually reduced over time in late training sessions, if the participant could perform the walking exercise. We utilized an assistive device to help the participant in making steps forward by the affected lower limbs (figure 1). Using this device, a physical therapist was able to provide assistance to the affected lower limb in hip and knee flexion and ankle dorsiflexion during swing phase by pulling a cable.[36] As an indicator of a low intensity exercise level, the target heart rate zone was between 30% and 40% of the heart rate reserve. The equation to calculate the heart rate reserve is [(maximum heart rate – resting heart rate) * % of targeted exercise intensity] + resting heart rate.[37] The maximum heart rate was determined using an age-predicted maximum heart rate (220 – participant's age),[37,38] and we subtracted 10 beats if the participant was on beta blocker medication.[39] The walking exercise started with two minutes of warming up at the speed of 0.6 mile/hour. The treadmill speed was then increased gradually until the heart rate reached the target heart rate zone. A session of walking exercise was ended with two minutes of cooling down. The duration of a walking exercise session was determined individually according to the participant's tolerance. It was initially set at 10 minutes and increased weekly by 5 minutes until the targeted duration of 30 minutes was reached for each session. An optical heart rate sensor (Polar OH1) was placed on participant's non-affected forearm to monitor heart rate continuously during the walking exercise. One physical therapist stood behind the participant to control trunk movement and to encourage the participant verbally. Another physical therapist operated the walking assistive device by pulling and releasing a cable to assist the affected leg/foot with every step forward.[36]

The blood pressure of the participant was monitored before, in the middle, and at the end of each exercise session to ensure safety. If the participant felt tired, the walking exercise would pause for two minutes while blood pressure of the participant was measured for safety purposes. At the end of each exercise session the participants were asked to rate the intensity of exercise using the 6 to 20 RPE scale. In a daily exercise log, we recorded the RPE, treadmill speed, percentage of body weight supported, and duration of the session after each exercise session. Each exercise session throughout the intervention process lasted approximately one hour, ranging from 30 to 60 minutes, including the time for set up.

Statistical Analysis

Descriptive statistics were used to summarize means, standard deviations, and confidence intervals for outcome measures. Paired t-test as well as Wilcoxon signed rank test were used to analyze within-group difference of pre- and post-intervention results using SPSS software (IBM SPSS statistics version 25). The significance level was set at 0.1 because of the sample size.[18]

Results

Ten non-ambulatory stroke survivors were enrolled into our study. One participant withdrew from the study after four weeks of the intervention due to family reasons. Data from nine participants were included in data analyses. Table 1 shows the participants' demographic and anthropometric data.

Significant ($p<0.1$) changes pre- and post-intervention were observed in measured parameters (table 2). HbA1c decreased from 6.1±0.9 to 5.6±0.7 %.; rHR decreased from 72.6±11.5 to 68.2±12.5 beats/minute; systolic blood pressure (SBP) decreased from 143±14.1 to 134.1±18.6 mmHg; diastolic blood pressure (DBP) decreased from 86.9±11.1 to 82.3±6.8 mmHg. Scores on the PHQ-9 decreased from 7.78±6.57 to 3.33± 2.87. The effect size for those significant differences were 1.05 (HbA1c), 1.67 (rHR), 1.05 (SBP), and 0.37 (DBP). The mean values of LDL showed a trend to decrease, from 103.1±23.1 mg/dl to 101.4±22.8 mg/dl, although the difference was not statistically significant ($p=0.37$).

The mean value of RPE showed a trend to decrease, from 13.9 ± 3.1 at pre-intervention, to 13.0 ± 3.8 at post-intervention, however this decrease was not significant ($p=0.55$, table 3). The mean values of body weight and body mass index changed significantly ($p<0.1$) from 192.6±45.7 lbs. and 28.7±8.2 kg/m^2 pre-intervention to 189.3±45.4 lbs. and 28.1±8.0 kg/m^2 post intervention. The means of body weight support, duration of session, and treadmill speed during the first session of the aerobic walking training were 40 ± 0.0%, 6.8 ± 6.4 minutes, and 0.6 ± 0.1 mile per hour (MPH), respectively. At the last training session those mean values were changed significantly ($p<0.1$) to 10.6 ± 6.8%, 29.6 ± 0.9 minutes, and 1.02 ± 0.1 MPH; respectively. The participants reported no changes in their medications or diet habits during the intervention period. The results were similar when we utilized Wilcoxon signed rank test (nonparametric) and paired t-test (parametric).

Discussion

In this pilot study, after an 8-week low intensity aerobic walking exercise we observed significant improvement in measures of accumulated glucose level (HbA1c), resting heart rate (rHR), blood pressure (DBP and SBP), and PHQ-9 in a group of chronic non-ambulatory stroke survivors. These results may be partially due to the use of a unique assistive walking device in our study. The moderate to high exercise intensity (40 % to 70% of heart rate reserve) has been recommended to improve physical health in stroke survivors with mild or moderate impairment.[6] However, our participants were severely disabled non-ambulatory stroke survivors. Considering their safety and tolerance, we controlled the intensity of their walking exercise at a low level (i.e. between 30% and 40% of the heart rate reserve). Considering the resultant RPE of the walking exercise (the average RPE of 13.9 in the first training session and 13.0 at the last training session) on the other hand, indicated a moderate intensity of exercise.[40] The RPE level of 11 to 14 corresponded to exercise intensity previously indicated to positively affect cardiovascular health.[6,41] The results of the current study confirmed that, even though designed initially for a low intensity, our walking exercise was able to sufficiently stress the cardiovascular system to induce significant changes in measured parameters. Such results may be due to the activation and loading of the non-affected side as it is well known that during walking exercise stroke survivors can actively load the lower limb of the non-affected side.[41] However, the activation and loading on the non-affected side may not be sufficient. A study of robot-assisted gait training by van Nunen et al. (2012) reported that their walking exercise protocol could not reach the recommended exercise intensity to induce aerobic effects in severely impaired stroke survivors.[42] One of the major limitations of the study by van Nunen et al. (2012) could be that their robotic gait training device provided excessive assistance and therefore limited the active engagement of the affected lower limb of the stroke survivors during gait training.[36] The assistive walking device used in our study has a unique design in that it provides minimal assistance to the affected lower limb and therefore encourages the activation and loading of the affected lower limb during walking exercise.

Our intervention might help participants to reduce their risk of recurrent stroke or development of diabetes as indicated by the decrease in HbA1c level. According to the American Diabetes Association, people who have HbA1c between 5.7 and 6.4% are considered prediabetic,[43] while the World Health Organization considers those with HbA1c between 6 and 6.5% as prediabetic and recommends starting a diabetes prevention program.[44] Our intervention reduced the mean of HbA1c and might move our participants from being prediabetic to non-diabetic (below 5.7%). Specifically, four participants in this study changed from pre-diabetic category to non-diabetic category based on their HbA1c values. The mean difference in HbA1c was 0.44%, and a change of 0.5% is considered a clinically meaningful change.[45] Stroke survivors who had HbA1c >6% were at higher risk of recurrent stroke,[46] and people with ischemic stroke who have diabetes experience a poor prognosis.[47] Wang et al.[23] investigated the effect of 6 weeks (3 sessions/week) of low intensity exercise using an ergometer cycle on glucose tolerance in non-ambulatory stroke survivors. They reported an improvement in all of glucose tolerance indices in the intervention group.[23] However, they conducted their study during subacute stage of stroke and recruited non-diabetic stroke survivors. In addition, their intervention and outcome measures are different than ours since our intervention was 8-weeks of low intensity aerobic walking exercise, and we measured HbA1c which provides the average reading of glucose level during the previous 8 to 12 weeks.[31] In addition, three participants in our study were diagnosed with type 2 diabetes mellitus. Therefore, it is hard to make a comparison between the results from Wang et al.[23] study and our results. We believe recruiting a large sample of diabetic and non-diabetic subacute and chronic non-ambulatory stroke survivors into a randomized control trial will provide us with more definite results on the effect of an aerobic walking exercise on glucose indices.

We can only compare our result on HbA1c to the findings from ambulatory stroke survivors due to the lack of past studies that examined the effect of aerobic walking exercise on the risk of diabetes mellitus in non-ambulatory stroke survivors. Ivey et al.[4] reported the improvement of glucose tolerance and insulin sensitivity in chronic ambulatory stroke survivors following six months (3 sessions/week) of treadmill walking training. Tang et al.[48] investigated the effect of 6-month mixed exercises (3 sessions/week) with high (intervention group) or low (control group) intensities in chronic ambulatory stroke survivors. They reported significant changes in fasting glucose level after the intervention in both groups.[48] Although our participants were more severely impaired and our intervention duration was relatively short compared to those two past studies, we still observed an improvement in the measurement of HbA1c, indicating a great potential of our walking exercise intervention for glycemic control. HbA1c is a better measurement of glucose level than fasting glucose measurement since it provides an average reading of glucose level for the past 8 to 12 weeks and therefore minimizing the influence of a short-term fluctuation in glucose level.[31]

An observed improvement in rHR in the current study may be partially attributed to an improvement in fitness level and/or due to changes in autonomic nervous system. Improving fitness level is related to decrease in rHR.[49] We did not directly measure maximum oxygen consumption, a commonly used indicator of fitness level. However, significant changes before and after the intervention in body weight support, duration of walking exercise session, treadmill speed, and body mass index clearly imply an improvement in fitness level. In addition, stroke survivors may present an impaired autonomic nervous system as a consequence of stroke.[50] Past studies have demonstrated that aerobic exercise is an effective modality in reducing activities of the sympathetic nervous system and enhancing activities of the parasympathetic nervous system.[26,51] Our walking exercise intervention might have improved autonomic nervous system function leading to a decrease in rHR. However, we did not have any direct measurement to confirm such interpretation. Nevertheless, our intervention reduced mean rHR from 72.6 to 68.2 bpm, which is clinically significant in stroke survivors. Past studies suggested that stroke survivors with rHR > 70 bpm would be at higher risk of fatal or non-fatal myocardial infarction [52] and death [53] when compared to stroke survivors with rHR < 70 bpm.

The results of the current study support our choice of the intensity and duration of the walking exercise. In designing the current study, we did not utilize graded maximal exercise test to determine the maximum heart rate because the severity of stroke of the participants, and it was not recommended if a low intensity exercise are used.[6] Instead, we estimated the maximal heart rate of each participant using the age-predicted maximum heart rate (220 – participant's age) which is commonly used in research,[54] and subsequently estimated the heart rate reserve based on the targeted exercise intensity.[37] The commonly-used equation for maximal heart rate has been questioned in terms of underestimating maximal heart rate in healthy older adults, leading to the effect of underestimating the true level of physical stress imposed during exercise testing.[54] When applying the equation to stroke survivors, true physical stress may even further be underestimated because stroke survivors are less physically fit than healthy older adults.[55] As mentioned above, the recorded data of RPE during the walking exercise indicate that the participants in the current study were in fact exercising at a moderate intensity, even though our initial design using the estimated heart rate reserve was a low intensity exercise. A past study by Rimmer et al.[56] reported significant decreases in SBP (10.3 mmHg) and DBP (8.7 mmHg) after a mixed exercise program with moderate intensity in ambulatory chronic stroke survivors, but not after an aerobic exercise with low intensity. Another past study by Potempa et al.[57] reported significant decreases in SBP by 7 mmHg and DBP by 4 mmHg after 10-week of leg cycle ergometer exercises (3 session/week) in chronic stroke survivors with moderate impairments. The mean decreases of 8.9 mmHg in SBP and 4.6 mmHg in DBP observed in our participants after the walking exercise were comparable to the changes reported by Rimmer et al.[56] and Potempa et al.[57], despite the fact that our participants were severely disabled. In terms of intervention duration, past studies have suggested that the duration of at least 8 weeks of aerobic walking exercise is required to affect cardiovascular health positively.[3] Some past studies reported no significant improvement in rHR or blood pressure in non-ambulatory stroke survivors after short durations (2 to 3 weeks) of walking training using body weight support system and robotic assistive device.[26,27] The longer duration, 8 weeks, of walking exercise in our study might be the reason for the significant improvement in outcome measures.

Although not statistically significant, there is a trend in our data for a decrease in LDL, with six out of nine of our participants showing a decrease in LDL post intervention. The lack of significant differences in the LDL measurement could be due to the use of low intensity exercise in the current study. Past studies have recommended high intensity of aerobic exercise to significantly lower LDL.[58,59] In addition, we did not control for the participants' diet, which might have affected the results.

Our results indicate that the walking exercise program may help stroke survivors in managing their depression. Depression is common in stroke survivors and negatively affects cardiovascular system and quality of life.[60] [61] Literature has reported that risk factors of depression after stroke include female gender and young age,[62] left hemisphere lesion,[63] and non-ambulatory status of stroke survivors.[64] Our participants were all non-ambulatory and almost all had brain lesions in the left hemisphere of the brain, and therefore were prone to depression. Before our intervention, the mean score of the PHQ-9 for our participants was 7.78±6.57 indicating a mild depression.[65] After the intervention, the mean score of PHQ-9 for our participants was 3.33±2.87 indicating a minimal or no depression.[65] Aerobic exercise has been demonstrated to be an effective intervention in improving symptoms of depression.[66] Our intervention may help non-ambulatory stroke survivors to better manage their symptoms of depression and promote their participation in rehabilitation programs since depression is a dominant barrier for stroke survivors for participation in rehabilitation therapy programs.[55]

Our study has several limitations. First, the small sample size and lack of a control group limit the internal and external validity of our study. In addition, we did not control for diet during our intervention period which might have influenced some of our results,[67] even though all participants reported no changes in their dietary habits during their participation in our study. Furthermore, we did not objectively measure daily activities of our participants throughout the intervention period. However, we collected a weekly physical activity log from each participant. No one reported performing any aerobic exercise at home. Most of their reported activities were stretching, balance, and hand-therapy exercise.

Conclusion

Our results show that eight weeks of aerobic walking exercise may modify cardiovascular risk factors in non-ambulatory stroke survivors. Future randomized control studies with larger sample size are needed to confirm our pilot findings.

Table 1: Participants characteristics.

Age (years) (range: min - max)	61.8 ± 13.6 (40 – 78)
Men/women	5/4
Stroke type: Ischemic/hemorrhagic	8/1
Hemiparetic side: Left/right	1/8
Time since stroke (months)	27.0 ± 14.3 (7 – 52)
Race: White/African American	6/3
Body mass index (kg/m^2) at baseline (range: min - max)	28.7±8.2 (15.7 – 42.8)
Hypertension: Yes/no	8/1
Diabetes mellitus: Yes/no	3/6
Smoker: Yes/no	1/8
Medications: Yes/no	
Diabetes:	3/6
Beta blockers:	3/6
Other blood pressure:	8/1
Lipids lowering:	6/3

min: minimum, max: maximum.

Table 2: Outcome measures for cardiovascular risk factors.

	Pre-intervention	Post-intervention	Mean Differences	Effect size	90% confidence interval		p-value
					Lower	Upper	
HbA1c (%)	6.1 ± 0.9	5.6 ± 0.7	0.44	1.05	0.19	0.7	0.01*
rHR (bpm)	72.6 ± 11.5	68.2 ± 12.5	4.33	1.67	2.72	5.94	<0.001*
SBP (mmHg)	143 ± 14.1	134.1 ± 18.6	8.89	1.05	3.63	14.14	0.01*
DBP (mmHg)	86.9 ± 11.1	82.3 ± 6.8	4.56	0.73	0.71	8.4	0.03*
LDL (mg/dl)	103.1 ± 23.1	101.4 ± 22.8	1.72	0.12	- 7.48	10.93	0.37
PHQ-9	7.78 ± 6.57	3.33 ± 2.87	4.44	1.01	1.72	7.17	0.02**

HbA1c: glycated hemoglobin, rHR: resting heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low-density lipoprotein, PHQ-9: patient health questionnaire-9.

* statistically significant ($p < 0.1$), (one tailed).

** statistically significant ($p < 0.1$), (two tailed).

Table 3: Exercise outcome measures.

	Pre-intervention	Post-intervention	Mean Differences	Effect size	90% confidence interval		p-value
					Lower	Upper	
RPE◆	13.9 ± 3.1	13.0 ± 3.8	0.89	0.21	-1.79	3.56	0.55
Body weight (lbs.)	192.6 ± 45.7	189.3 ± 45.4	3.30	1.19	1.58	5.02	0.01*
BMI (kg/m2)	28.7 ± 8.2	28.1 ± 8.0	0.59	1.15	0.27	0.90	0.01*
Treadmill speed (MPH) ◆	0.6 ± 0.1	1.02 ± 0.1	-0.38	-4.53	-0.43	-0.33	<0.001*
Walking duration (minutes) ◆,^	6.8 ± 6.4	29.6 ± 0.9	-22.78	-3.58	-26.72	-18.84	<0.001*
% of body weight support◆	40 ± 0.0	10.6 ± 6.8	29.44	4.32	25.22	33.67	<0.001*

RPE: 6 to 20 Borg rating of perceived exertion scale, lbs.: pounds, BMI: body mass index, kg/ m^2: kilogram per square meter, MPH: mile per hour, %: percentage.

◆ These values are the means obtained by the end of the first aerobic walking exercise session and by the end of the last aerobic walking exercise session (post-intervention).

^ Walking duration: the walking time that was within targeted heart rate zone.

* statistically significant ($p < 0.1$), (two tailed).

Figure 1: The assistive device used to assist the participants in hip flexion and ankle dorsiflexion at the swing phase of a gait cycle on the affected side.

References

1. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-1623.

2. Lennon O, Blake C. Cardiac rehabilitation adapted to transient ischaemic attack and stroke (CRAFTS): a randomised controlled trial. *BMC neurology.* 2009;9:9.

3. Ivey FM, Hafer-Macko CE, Macko RF. Exercise training for cardiometabolic adaptation after stroke. *J Cardiopulm Rehabil Prev.* 2008;28(1):2-11.

4. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke.* 2007;38(10):2752-2758.

5. Vermeer SE, Sandee W, Algra A, et al. Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. *Stroke.* 2006;37(6):1413-1417.

6. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(8):2532-2553.

7. Wang A, Chen S, Wang C, et al. Resting heart rate and risk of cardiovascular diseases and all-cause death: the Kailuan study. *PLoS One.* 2014;9(10):e110985.

8. Hornnes N, Larsen K, Boysen G. Little change of modifiable risk factors 1 year after stroke: a pilot study. *International journal of stroke : official journal of the International Stroke Society.* 2010;5(3):157-162.

9. Friday G, Alter M, Lai SM. Control of hypertension and risk of stroke recurrence. *Stroke.* 2002;33(11):2652-2657.

10. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. *Stroke.* 2014;45(8):2506-2513.

11. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Stroke.* 2004;35(5):1230-1240.

12. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. *Stroke research and treatment.* 2012;2012:959120.

13. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *Jama.* 2000;284(22):2901-2906.

14. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016;47(2):581-641.

15. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(1):315-353.

16. Stoller O, de Bruin ED, Knols RH, Hunt KJ. Effects of cardiovascular exercise early after stroke: systematic review and meta-analysis. *BMC neurology.* 2012;12:45.

17. Mackay-Lyons MJ, Makrides L. Exercise capacity early after stroke. *Archives of physical medicine and rehabilitation.* 2002;83(12):1697-1702.

18. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: A mixed-methods systematic review and meta-analysis. *Brain Behav.* 2018;8(7):e01000.

19. Wade D. Rehabilitation therapy after stroke. *Lancet.* 1999;354(9174):176-177.

20. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8(8):741-754.

21. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *The Cochrane database of systematic reviews.* 2016;3:CD003316.

22. Stoller O, Schindelholz M, Bichsel L, et al. Feedback-controlled robotics-assisted treadmill exercise to assess and influence aerobic capacity early after stroke: a proof-of-concept study. *Disability and rehabilitation Assistive technology.* 2014;9(4):271-278.

23. Wang Z, Wang L, Fan H, Lu X, Wang T. Effect of low-intensity ergometer aerobic training on glucose tolerance in severely impaired nondiabetic stroke patients. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2014;23(3):e187-193.

24. Wang Z, Wang L, Fan H, et al. Adapted low intensity ergometer aerobic training for early and severely impaired stroke survivors: a pilot randomized controlled trial to explore its feasibility and efficacy. *Journal of physical therapy science.* 2014;26(9):1449-1454.

25. Han EY, Im SH, Kim BR, Seo MJ, Kim MO. Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial. *Medicine (Baltimore).* 2016;95(41):e5078.

26. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. *Neurorehabilitation and neural repair.* 2012;26(4):318-324.

27. Teixeira da Cunha Filho I, Lim PA, Qureshy H, Henson H, Monga T, Protas EJ. A comparison of regular rehabilitation and regular rehabilitation with supported treadmill ambulation training for acute stroke patients. *Journal of rehabilitation research and development.* 2001;38(2):245-255.

28. Mehrholz J, Werner C, Hesse S, Pohl M. Immediate and long-term functional impact of repetitive locomotor training as an adjunct to conventional physiotherapy for non-ambulatory patients after stroke. *Disability and rehabilitation.* 2008;30(11):830-836.

29. Hoyer E, Jahnsen R, Stanghelle JK, Strand LI. Body weight supported treadmill training versus traditional training in patients dependent on walking assistance after stroke: a randomized controlled trial. *Disability and rehabilitation.* 2012;34(3):210-219.

30. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Physical therapy.* 1986;66(10):1530-1539.

31. Ang SH, Thevarajah M, Alias Y, Khor SM. Current aspects in hemoglobin A1c detection: a review. *Clin Chim Acta.* 2015;439:202-211.

32. Zhang X, Shi Q, Zheng H, et al. Prevalence of Abnormal Glucose Regulation according to Different Diagnostic Criteria in Ischaemic Stroke without a History of Diabetes. *BioMed research international.* 2018;2018:8358724.

33. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama.* 1999;282(18):1737-1744.

34. Williams LS, Brizendine EJ, Plue L, et al. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke.* 2005;36(3):635-638.

35. Prisnie JC, Fiest KM, Coutts SB, et al. Validating screening tools for depression in stroke and transient ischemic attack patients. *Int J Psychiatry Med.* 2016;51(3):262-277.

36. Liu W. A narrative review of gait training after stroke and a proposal for developing a novel gait training device that provides minimal assistance. *Topics in stroke rehabilitation.* 2018;25(5):375-383.

37. Billinger SA, Boyne P, Coughenour E, Dunning K, Mattlage A. Does aerobic exercise and the FITT principle fit into stroke recovery? *Current neurology and neuroscience reports.* 2015;15(2):519.

38. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.

39. Floel A, Werner C, Grittner U, et al. Physical fitness training in Subacute Stroke (PHYS-STROKE)--study protocol for a randomised controlled trial. *Trials.* 2014;15:45.

40. Ammann BC, Knols RH, Baschung P, de Bie RA, de Bruin ED. Application of principles of exercise training in sub-acute and chronic stroke survivors: a systematic review. *BMC neurology.* 2014;14:167.

41. Stoller O, de Bruin ED, Schindelholz M, Schuster-Amft C, de Bie RA, Hunt KJ. Efficacy of Feedback-Controlled Robotics-Assisted Treadmill Exercise to Improve Cardiovascular Fitness Early After Stroke: A Randomized Controlled Pilot Trial. *Journal of neurologic physical therapy : JNPT.* 2015;39(3):156-165.

42. van Nunen MP, Gerrits KH, de Haan A, Janssen TW. Exercise intensity of robot-assisted walking versus overground walking in nonambulatory stroke patients. *Journal of rehabilitation research and development.* 2012;49(10):1537-1546.

43. Chamberlain JJ, Rhinehart AS, Shaefer CF, Jr., Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. *Annals of internal medicine.* 2016;164(8):542-552.

44. WHO Guidelines Approved by the Guidelines Review Committee. In: *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation.* Geneva: World Health Organization Copyright (c) World Health Organization 2011.; 2011.

45. Lenters-Westra E, Schindhelm RK, Bilo HJ, Groenier KH, Slingerland RJ. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. *The Netherlands journal of medicine.* 2014;72(9):462-466.

46. Wu S, Shi Y, Wang C, et al. Glycated hemoglobin independently predicts stroke recurrence within one year after acute first-ever non-cardioembolic strokes onset in A Chinese cohort study. *PLoS One.* 2013;8(11):e80690.

47. Jing J, Pan Y, Zhao X, et al. Prognosis of Ischemic Stroke With Newly Diagnosed Diabetes Mellitus According to Hemoglobin A1c Criteria in Chinese Population. *Stroke.* 2016;47(8):2038-2044.

48. Tang A, Eng JJ, Krassioukov AV, et al. Exercise-induced changes in cardiovascular function after stroke: a randomized controlled trial. *International journal of stroke : official journal of the International Stroke Society.* 2014;9(7):883-889.

49. Plasqui G, Westerterp KR. Accelerometry and heart rate as a measure of physical fitness: proof of concept. *Medicine and science in sports and exercise.* 2005;37(5):872-876.

50. Al-Qudah ZA, Yacoub HA, Souayah N. Disorders of the Autonomic Nervous System after Hemispheric Cerebrovascular Disorders: An Update. *J Vasc Interv Neurol.* 2015;8(4):43-52.

51. Goldsmith RL, Bloomfield DM, Rosenwinkel ET. Exercise and autonomic function. *Coron Artery Dis.* 2000;11(2):129-135.

52. Fox K, Bousser MG, Amarenco P, et al. Heart rate is a prognostic risk factor for myocardial infarction: a post hoc analysis in the PERFORM (Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack) study population. *International journal of cardiology.* 2013;168(4):3500-3505.

53. Bohm M, Cotton D, Foster L, et al. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *European heart journal.* 2012;33(22):2804-2812.

54. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol.* 2001;37(1):153-156.

55. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and

Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Circulation.* 2004;109(16):2031-2041.

56. Rimmer JH, Rauworth AE, Wang EC, Nicola TL, Hill B. A preliminary study to examine the effects of aerobic and therapeutic (nonaerobic) exercise on cardiorespiratory fitness and coronary risk reduction in stroke survivors. *Archives of physical medicine and rehabilitation.* 2009;90(3):407-412.

57. Potempa K, Lopez M, Braun LT, Szidon JP, Fogg L, Tincknell T. Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke.* 1995;26(1):101-105.

58. Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. *Lipids Health Dis.* 2017;16(1):132.

59. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports medicine (Auckland, NZ).* 2014;44(2):211-221.

60. Towfighi A, Ovbiagele B, El Husseini N, et al. Poststroke Depression: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2017;48(2):e30-e43.

61. Ivanovs R, Kivite A, Ziedonis D, Mintale I, Vrublevska J, Rancans E. Association of depression and anxiety with cardiovascular co-morbidity in a primary care population in Latvia: a cross-sectional study. *BMC Public Health.* 2018;18(1):328.

62. Karamchandani RR, Vahidy F, Bajgur S, et al. Early depression screening is feasible in hospitalized stroke patients. *PLoS One.* 2015;10(6):e0128246.

63. Jeong YJ, Kim WC, Kim YS, Choi KW, Son SY, Jeong YG. The Relationship between Rehabilitation and Changes in Depression in Stroke Patients. *Journal of physical therapy science.* 2014;26(8):1263-1266.

64. Kauhanen M, Korpelainen JT, Hiltunen P, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke.* 1999;30(9):1875-1880.

65. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.

66. Blumenthal JA, Smith PJ, Hoffman BM. Is Exercise a Viable Treatment for Depression? *ACSMs Health Fit J.* 2012;16(4):14-21.

67. Kristo AS, Matthan NR, Lichtenstein AH. Effect of diets differing in glycemic index and glycemic load on cardiovascular risk factors: review of randomized controlled-feeding trials. *Nutrients.* 2013;5(4):1071-1080.

Chapter 5: Changes in bone biomarkers after an 8-week walking exercise in non-ambulatory stroke survivors: A pilot study

Abstract

Background: Stroke survivors are at high risk of osteoporosis and bone fracture. Compared to healthy people, stroke survivors are less active, and they tend to unload their bones of their affected lower limb causing rapid increases in bone loss. Non-ambulatory stroke survivors are largely losing bone health when compared to stroke survivors who walk independently. Yet, most previous studies have been conducted on ambulatory stroke survivors. Thus, in this study we aimed to investigate the effect of aerobic walking exercise on bone health in non-ambulatory stroke survivors using a treadmill, a body weight support system, and a walking training device.

Methods: We recruited nine non-ambulatory stroke survivors (age: 61.8 ± 13.6 years, 5 men, 8 with ischemic stroke). They completed the aerobic walking exercise program (three sessions/week for eight weeks). Serum concentration of markers of bone turnover, osteocalcin (OC) and carboxy-terminal telopeptide of type I collagen (ICTP), were measured pre- and post-intervention.

Results: OC increased significantly from 8.51±2.28 ng/ml to 9.39±2.97 ng/ml ($p = 0.09$). Also, ICTP increased significantly from 4.45±2.58 ng/ml to 5.31±2.92 ng/ml ($p = 0.02$).

Conclusions: The results suggest that the low intensity aerobic walking exercise may improve bone health by increasing bone formation markers. However, the initial severe disability of the participants and the nature of the aerobic walking exercise may initiate the bone remodeling process slowly.

Key words

Bone, non-ambulatory stroke, walking, bone formation, bone resorption

Introduction

Osteoporosis and bone fracture are common complications reported in stroke survivors.[1,2] Loss of bone mineral density is noticed largely within six months of stroke onset and is associated with vascular elasticity, motor impairments, reduced fitness level, and functional limitations after stroke.[3-7] In the affected side, immobility and reduced load on the bone lead to bone loss and increase the risk of bone fracture in stroke survivors [7-9] who are at high risk of osteoporosis during the first year post-stroke when compared to healthy individuals.[10] During the first year post-stroke, bone mineral density and lean mass of muscles are lower in the affected lower limb when compared to non-affected lower limb.[8,11] In addition, stroke survivors have significant lower levels of bone formation markers and significantly higher levels of bone resorption markers when compared to healthy controls.[4]

Non-ambulatory stroke survivors are at an even higher risk of bone loss and may benefit from loading exercise such as walking. Non-ambulatory stroke survivors showed a 4-fold loss in bone mineral density compared with ambulatory stroke survivors within the first year post-stroke.[9] Loading exercise, such as walking, is important to prevent bone loss.[12] Loading on bones during walking can help maintain bone density by stimulating factors of bone formation.[2,12] Walking exercise using a body weight support increased bone formation markers and decreased levels of bone resorption markers in people with spinal cord injury.[13] To our knowledge, there is no study that has investigated the effect of walking exercise on bone health in non-ambulatory stroke survivors who score 2 or less on functional ambulation category (FAC).[14]

The objectives of this pilot study were to examine possible changes in bone biomarkers and possible changes in motor function as measured by FAC and Berg Balance Scale (BBS) after eight weeks of walking exercise in a group of non-ambulatory stroke survivors.

Materials and methods

Study design

This pilot study was conducted in a single group. The intervention was an 8-week walking exercise program with three sessions per week. Bone formation and resorption biomarkers were assessed pre- and post-intervention. We recruited 10 non-ambulatory stroke survivors, and they: 1) scored ≤ 2 on FAC, 2) were between 18 and 80 years of age, 3) had a stroke less than 5 years ago, 4) walked independently before the stroke, 5) were able to follow directions in English, and 6) were able to attend all of our intervention sessions. We excluded stroke survivors who had osteoporosis before stroke, and those who currently had renal disease, unstable medical conditions, or musculoskeletal disorders which might prevent the participant from doing our intervention. Informed consent was obtained from all participants, and our study was approved by the institutional review board (IRB) of the University of Kansas Medical Center (KUMC).

Measurements

On the pre- and post-intervention assessment days, the participant came to our research laboratory after fasting for 12 hours. The blood sample of 30 mL was collected between 8 and 10 a.m. by a registered nurse from the antecubital vein in the unaffected arm into BD Vacutainer serum blood collection tubes (red top tubes). Within 30 minutes, after the collected blood clotted, the tube was centrifuged at 2,500 g for 10 minutes at room temperature, to separate serum. Serum was transferred into a clean tube and stored at -80° C for future analysis. Each blood sample was coded, and it had no identifiable subject information. In analyzing the blood sample, serum concentration of markers of bone turnover, osteocalcin (OC) and carboxy-terminal telopeptide of type I collagen (ICTP) were determined using Osteocalcin Human ELISA Kit (Thermo Fisher Scientific Inc., Waltham, MA, USA; catalog #: KAQ1381) and Human ICTP ELISA Kit (Aviva Systems Biology, San Diego, USA; catalog #: OKEH00680), respectively.

Serum OC level is correlated with bone formation rate.[15] OC has been one of the surrogate markers used to describe the effects of anti-osteoporotic drugs.[16,17] When compared to other bone resorption markers, ICTP, which is degraded by matrix-metalloproteases (MMPs), has a higher sensitivity and accuracy as a screening tool for bone resorption in people with lung cancer,[18,19] and had a higher correlation with changes in bone mineral density in postmenopausal women.[20] We utilized serum rather than urine in measuring the concentrations of OC and ICTP because serum markers have less day to day variability.[15]

After the blood sample was taken, a trained physical therapist scored FAC and BBS for the participant. The FAC uses a classification system of six categories. The lowest classification is Category 1 which indicates nonfunctional ambulation and the highest classification is Category 6 which indicates independent ambulation on varying surfaces.[14] Category 2 indicates a need of continued contact assistance from one person for an individual to walk safely.[14] FAC is a reliable and a valid measure in stroke survivors.[21] The BBS is a test of individual's balance consisting of 14 items. These items evaluate sitting, standing, and weight transfer activities that are each scored on a 5-point scale.[22] The BBS has a maximum score of 56, with higher values signifying better balance. The inter-rater and intra-rater reliability of the BBS have been found to be high within stroke patients.[23]

Aerobic walking exercise

During aerobic walking exercise, a participant walked on a treadmill for about 30 minutes, three times per week for eight weeks. A harness was attached to the ceiling and was tightened around participant's waist, thighs and hips to support partial body weight and protect the participant from falling. About 40% of the participant's weight was supported initially at the first training session. The body weight support was gradually reduced over time in late training sessions, if the participant could perform the walking exercise. We utilized an assistive device to help the participant in making steps forward by the affected lower limbs (Figure 1). Using this device, a physical therapist was able to provide the affected lower limb with assistance in hip and knee flexion and ankle dorsiflexion during swing phase by pulling a cable.[24] To reach a low intensity exercise, the target heart rate zone was between 30% and 40% of exercise intensity using the heart rate reserve. The equation to calculate the heart rate reserve is the following: [(maximum heart rate – resting heart rate) * % of targeted exercise intensity] + resting heart rate.[25] The maximum heart rate was determined using an age-predicted maximum heart rate (220 – participant's age),[25,26] and we subtracted 10 beats if the participant was on a beta blocker medication.[27] The walking exercise started with two minutes of warming up at the speed of 0.6 mile/hour. The treadmill speed was then increased gradually until the heartrate reached the target heart rate zone. We ended a session of walking exercise with two minutes of cooling down. The duration of a walking exercise session was determined individually according to the participant's tolerance. It was initially set at 10 minutes and increased weekly by 5 minutes until the targeted duration of 30 minutes was reached for each session. An optical heart rate sensor (Polar OH1) was placed on participant's non-affected forearm to monitor heart rate continuously during the walking exercise. One physical therapist stood behind the participant to control trunk movement and to encourage the participant verbally. Another physical therapist operated the walking assistive device by pulling and releasing a cable to assist every step forward of the affected leg/foot.[24] Blood pressure of the participant was monitored before, in the middle, and at the end of each exercise session to ensure safety. If the participant felt tired, we would pause the walking exercise for two minutes and measured the blood pressure of the participant for safety purposes. At the end of each exercise session we asked the participants to rate the intensity of exercise using the 6 to 20 RPE scale. In a daily exercise log, we recorded the RPE, treadmill speed, percentage of body weight supported, and duration of the session after each exercise session.

Each exercise session throughout the intervention process lasted approximately one hour, ranging from 30 to 60 minutes, including the time for set up.

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences for Windows (SPSS) (Version 25, Armonk, NY; IBM Corp). Descriptive statistics were utilized to report means, standard deviations, and confidence intervals for all outcome measures. Paired t-test as well as Wilcoxon signed rank test were used to compare post-intervention data to pre-intervention data. Alpha was set at 0.1 due to limited sample size [28] (one tailed for OC and ICTP) and (2 tailed for FAC and BBS).

Results

Ten non-ambulatory stroke survivors were recruited and consented to participate in our study. Due to family reasons, one of the participants withdrew from the study. Nine participants (age: 61.8 ± 13.6, 5 men, 8 with ischemic stroke) completed all exercise and assessment sessions; and their results were included in the analysis. Table 1 shows the participants characteristics before the intervention. When comparing pre-intervention to post-intervention results, OC increased significantly ($p<0.1$) from 8.51 ± 2.28 ng/ml to 9.39 ± 2.97 ng/ml, and ICTP increased significantly ($p<0.1$) from 4.45 ± 2.58 ng/ml to 5.31 ± 2.92 ng/ml (table 2). Specifically, OC level increased in 5 out of 9 participants, and ICTP level increased in 6 out of 9 participants. FAC and BBS also increased significantly ($p<0.1$) from 1.0 to 1.33, and from 7.22 ± 10.02 to 15.78 ± 14.81; respectively. The results were similar when we utilized Wilcoxon signed rank test (nonparametric) and paired t-test (parametric).

Discussion

In this pilot study, both a bone formation marker (OC) and a bone resorption maker (ICTP) significantly increased after the 8-week walking exercise in a group of non-ambulatory stroke survivors. We expected an increase in OC and a decrease in ICTP. The observed increase in ICTP in our results was unexpected. Our results suggest that bone remodeling is taking place in our study participants and it is likely triggered by the exercise. The bone remodeling is a dynamic process, with bone resorption and formation events taking place simultaneously and asynchronously in different places in the skeleton.

The aerobic walking exercise may lead to enhanced bone formation as indicated by a significant increase in OC. OC is produced by osteoblasts and generally regarded as a marker of bone formation, with the majority of it being incorporated into the bone matrix but about 10% to 30% released into circulation.[29,30] No previous studies have reported changes in OC in non-ambulatory stroke survivors after walking exercise. The changes of 0.88 ng/ml in mean OC after 8 weeks (3 sessions/week) of walking exercise in the current study is comparable to similar studies in patients with spinal cord injury, if adjusting for similar duration of the exercise program. In people with paraplegia, a body weight supported gait training for 12 weeks (3 sessions/week) significantly increased the level of OC by 0.25 ng/ml.[31] In a group of adults with incomplete spinal cord injury, four months (3 sessions/week) of assisted walking with functional electrical stimulation increased the level of OC by 1.07 ng/ml.[32] Body weight supported gait training with neuromuscular electrical stimulation for six months (2 sessions/week) increased the level of OC by 3.78 ng/ml.[13] An important parameter in these past studies affecting the change of OC level is the duration of exercise program. In fact, it has been reported that six to 12 months [8] or more of weight bearing exercise [33] might be needed to demonstrate the significant improvement in bone mineral density. Future studies may examine the improvement in bone health using a longer duration of the aerobic walking exercise intervention in non-ambulatory stroke survivors.

The literature has indicated that the biomarker ICTP might respond to exercise programs differently over time. ICTP is the fragment of carboxy-terminal peptide of type I collagen released from bone matrix by MMPs, reflecting bone resorption.[18,34] In a study that tested the immediate effect of aerobic exercise in healthy young adults, ICTP significantly increased.[35] A past study showed that ICTP increased after one session of walking exercise, but decreased after one session of resistance exercise.[36] Improvements in bone health usually go through a bone remodeling process involving several phases that may take up to 6 months.[37,38] These phases include a bone resorption phase which lasts for two weeks, a reversal phase which lasts for nearly a month where both bone resorption markers and bone formation markers are present, and a bone formation phase which lasts for four months. The increased ICTP marker in the current study might imply an early stage of bone remodeling process occurred at the end of 8 weeks of walking exercise. Important reasons for such late initiation of bone remodeling process of the walking exercise program may include the slow progression in reducing body weight support throughout the 8-week intervention and the nature of aerobic exercise.

The type of exercise is an important factor in both the initiation and the progression of bone remodeling process. A study in older healthy women reported significant increase in bone mineral density after eight months of resistance exercise compared to eight months of aerobic exercise.[39] A single session of resistance exercise in older women with osteoporosis decreased the bone resorption marker compared to a single session of aerobic exercise.[36] Expectantly, aerobic exercise is less effective in loading and straining bones compared to resistance exercise.[36,39-41] However, given the severe sensorimotor impairment, resistance exercise generally is not feasible for non-ambulatory stroke survivors. Importantly, the results of the current study indicated the potential of aerobic walking exercise for improving bone health in non-ambulatory stroke survivors, even though at a slow pace. There are no exercise guidelines that recommend the optimal type of exercise to enhance bone health in stroke survivors.[33] Future research is needed to generate clinical evidence that may help developing specific exercise guidelines.

Some participants showed improvement in their walking ability after the intervention. All nine participants scored 1 on FAC at baseline indicating a need for the maximal assistance in walking. After the intervention, three of them improved their FAC scores to 2, which indicated that they need only manual contact to walk safely and to maintain balance. Improvement in walking ability after treadmill walking training in non-ambulatory stroke survivors has been reported in the literature.[42] In a study by Cho et al.,[43] a treadmill, body weight support system, and a robotic assistive device were used in gait training for non-ambulatory stroke survivors (3 sessions/week for four weeks). The mean difference of FAC reported in their study was 0.4, which is similar to the change of mean FAC observed in the current study (0.33).

Improved balance control in our participants could be related to their improved walking ability. Stroke survivors with severe impairments have impaired balance control, which is a barrier to locomotion and daily physical activities.[44] Walking ability is positively correlated with BBS in chronic stroke survivors.[45] Walking training is an effective modality to enhance balance in stroke survivors.[43,46] Walking exercise involves the unaffected lower limb, and can lead to improvement in balance in chronic stroke survivors who could walk independently.[44] In non-ambulatory stroke survivors, dynamic standing therapy [47] and gait robotic gait training [43] can improve balance measured by BBS. During our intervention, the participants are forced to fully load their unaffected lower limbs while maintaining a balance of their lower limbs and trunks. As a result, their balance control improved.

This study has several limitations. First, due to a small sample size and no control group, results of the current study should be interpreted with caution. Second, we utilized only one bone formation marker (OC) and one bone resorption marker (ICTP). Including more bone formation and resorption markers, as well as evaluation of bone density using imaging techniques, in future studies will provide researchers with a better picture of bone's response to walking exercise in non-ambulatory stroke survivors. Third, we did not control for medications that may affect bone quality such as vitamin D supplements.[2,48] In addition, we did not control for other medications such as some diabetic medications which might increase bone loss.[49] We also did not control for diet especially food that provide calcium or vitamin D. Finally, we did not control for other covariates that might affect the results of this study such as diabetes,[50] time since stroke, stroke severity,[51] sex hormones,[52] fitness level,[7] and season when collecting blood samples.[15]

Conclusion

The 8-week aerobic walking program may be an effective intervention in improving bone health, as shown by the increase in a bone formation marker levels observed in the current study. However, it seems that progression in initiating bone remodeling process was slow, probably due to the severe disability of the participants and the nature of aerobic exercise. Future studies with larger sample size and a control group are needed to confirm the findings of this pilot study.

Table 1: Participants characteristics.

Age (years) (range: min - max)	61.8 ± 13.6 (40 – 78)
Men/women	5/4
Stroke type: Ischemic/hemorrhagic	8/1
Hemiparetic side: Left/right	1/8
Time since stroke (months)	27 ± 14.3
Race: White/African-American/other	5/3/1
Body mass index (kg/m^2)	28.6 ± 8.2
Vitamin D supplements: Yes/no	5/4
Anti-depression drugs: Yes/no	4/5

min: minimum, max: maximum.

Table 2: Outcome measures.

	Pre-intervention	Post-intervention	Mean Differences	Effect size	90% CI of the Difference		p-value
					Lower	Upper	
OC (ng/ml)	8.51±2.28	9.39±2.97	0.88	0.48	-0.27	2.03	0.09*
ICTP (ng/ml)	4.45±2.58	5.31±2.92	0.87	0.90	0.27	1.47	0.02*
FAC	1±0	1.33±0.50	0.33	0.66	0.02	0.64	0.08**
BBS	7.22±10.02	15.78±14.81	8.56	1.57	5.17	11.94	< 0.01**

Mean ± standard deviation. CI: confidence interval, OC: osteocalcin, ng/ml: nanograms per milliliter, ICTP: carboxy-terminal telopeptide of type I collagen, FAC: functional ambulation category, BBS: Berg Balance Scale.
* statistically significant (1 tailed) (p = 0.1)
** statistically significant (2 tailed) (p = 0.1)

Figure 1: The assistive device used to assist the participants in hip flexion and ankle dorsiflexion at the swing phase of a gait cycle on the affected side.

References

1. Carda S, Cisari C, Invernizzi M, Bevilacqua M. Osteoporosis after stroke: a review of the causes and potential treatments. *Cerebrovasc Dis.* 2009;28(2):191-200.

2. Huo K, Hashim SI, Yong KL, Su H, Qu QM. Impact and risk factors of post-stroke bone fracture. *World J Exp Med.* 2016;6(1):1-8.

3. Pang MY, Yang FZ, Jones AY. Vascular elasticity and grip strength are associated with bone health of the hemiparetic radius in people with chronic stroke: implications for rehabilitation. *Physical therapy.* 2013;93(6):774-785.

4. Fisher A, Srikusalanukul W, Davis M, Smith P. Poststroke hip fracture: prevalence, clinical characteristics, mineral-bone metabolism, outcomes, and gaps in prevention. *Stroke research and treatment.* 2013;2013:641943.

5. Pang MY, Yang FZ, Lau RW, Cheng AQ, Li LS, Zhang M. Changes in bone density and geometry of the upper extremities after stroke: a case report. *Physiotherapy Canada Physiotherapie Canada.* 2012;64(1):88-97.

6. Borschmann K, Pang MY, Bernhardt J, Iuliano-Burns S. Stepping towards prevention of bone loss after stroke: a systematic review of the skeletal effects of physical activity after stroke. *International journal of stroke : official journal of the International Stroke Society.* 2012;7(4):330-335.

7. Pang MY, Eng JJ, McKay HA, Dawson AS. Reduced hip bone mineral density is related to physical fitness and leg lean mass in ambulatory individuals with chronic stroke. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2005;16(12):1769-1779.

8. Pang MY, Ashe MC, Eng JJ, McKay HA, Dawson AS. A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2006;17(11):1615-1625.

9. Jorgensen L, Jacobsen BK, Wilsgaard T, Magnus JH. Walking after stroke: does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2000;11(5):381-387.

10. Tomasevic-Todorovic S, Simic-Panic D, Knezevic A, Demesi-Drljan C, Maric D, Hanna F. Osteoporosis in patients with stroke: A cross-sectional study. *Ann Indian Acad Neurol.* 2016;19(2):286-288.

11. Jorgensen L, Jacobsen BK. Changes in muscle mass, fat mass, and bone mineral content in the legs after stroke: a 1 year prospective study. *Bone.* 2001;28(6):655-659.

12. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology.* 2012;2(2):1143-1211.

13. Carvalho DC, Garlipp CR, Bottini PV, Afaz SH, Moda MA, Cliquet A, Jr. Effect of treadmill gait on bone markers and bone mineral density of quadriplegic subjects. *Braz J Med Biol Res.* 2006;39(10):1357-1363.

14. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Physical therapy.* 1986;66(10):1530-1539.

15. Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. *The Clinical biochemist Reviews.* 2005;26(4):97-122.

16. Vergnaud P, Garnero P, Meunier PJ, Breart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. *J Clin Endocrinol Metab.* 1997;82(3):719-724.

17. Szulc P, Delmas PD. Biochemical markers of bone turnover: potential use in the investigation and management of postmenopausal osteoporosis. *Osteoporos Int.* 2008;19(12):1683-1704.

18. Kong QQ, Sun TW, Dou QY, et al. Beta-CTX and ICTP act as indicators of skeletal metastasis status in male patients with non-small cell lung cancer. *Int J Biol Markers.* 2007;22(3):214-220.

19. Tang C, Liu Y, Qin H, et al. Clinical significance of serum BAP, TRACP 5b and ICTP as bone metabolic markers for bone metastasis screening in lung cancer patients. *Clin Chim Acta.* 2013;426:102-107.

20. Yasumizu T, Hoshi K, Iijima S, Asaka A. Serum concentration of the pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) is a useful indicator of decline and recovery of bone mineral density in lumbar spine: analysis in Japanese postmenopausal women with or without hormone replacement. *Endocr J.* 1998;45(1):45-51.

21. Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. *Archives of physical medicine and rehabilitation.* 2007;88(10):1314-1319.

22. Berg K, Wood-Dauphine S, Williams J, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. *Physiotherapy Canada.* 1989;41(6):304-311.

23. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. *Canadian journal of public health = Revue canadienne de sante publique.* 1992;83 Suppl 2:S7-11.

24. Liu W. A narrative review of gait training after stroke and a proposal for developing a novel gait training device that provides minimal assistance. *Topics in stroke rehabilitation.* 2018;25(5):375-383.

25. Billinger SA, Boyne P, Coughenour E, Dunning K, Mattlage A. Does aerobic exercise and the FITT principle fit into stroke recovery? *Current neurology and neuroscience reports.* 2015;15(2):519.

26. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.

27. Floel A, Werner C, Grittner U, et al. Physical fitness training in Subacute Stroke (PHYS-STROKE)--study protocol for a randomised controlled trial. *Trials.* 2014;15:45.

28. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: A mixed-methods systematic review and meta-analysis. *Brain Behav.* 2018;8(7):e01000.

29. Li J, Zhang H, Yang C, Li Y, Dai Z. An overview of osteocalcin progress. *J Bone Miner Metab.* 2016;34(4):367-379.

30. Confavreux CB, Szulc P, Casey R, Varennes A, Goudable J, Chapurlat RD. Lower serum osteocalcin is associated with more severe metabolic syndrome in elderly men from the MINOS cohort. *Eur J Endocrinol.* 2014;171(2):275-283.

31. Mobarake BG, Banitalebi E, Ebrahimi A, Ghafari M. Effect of Progressive Locomotor Treadmill Compared to Conventional Training on Bone Mineral Density and Bone Remodeling in Paraplegia. *Middle East Journal of Rehabilitation and Health.* 2017;4(1).

32. Craven BC, Giangregorio LM, Alavinia SM, et al. Evaluating the efficacy of functional electrical stimulation therapy assisted walking after chronic motor incomplete spinal cord injury: effects on bone biomarkers and bone strength. *The journal of spinal cord medicine.* 2017;40(6):748-758.

33. Borschmann K. Exercise protects bone after stroke, or does it? A narrative review of the evidence. *Stroke research and treatment.* 2012;2012:103697.

34. Voorzanger-Rousselot N, Juillet F, Mareau E, Zimmermann J, Kalebic T, Garnero P. Association of 12 serum biochemical markers of angiogenesis, tumour invasion and bone turnover with bone metastases from breast cancer: a crossectional and longitudinal evaluation. *Br J Cancer.* 2006;95(4):506-514.

35. Wallace JD, Cuneo RC, Lundberg PA, et al. Responses of markers of bone and collagen turnover to exercise, growth hormone (GH) administration, and GH withdrawal in trained adult males. *The Journal of clinical endocrinology and metabolism.* 2000;85(1):124-133.

36. Gombos GC, Bajsz V, Pek E, et al. Direct effects of physical training on markers of bone metabolism and serum sclerostin concentrations in older adults with low bone mass. *BMC Musculoskelet Disord.* 2016;17:254.

37. Hadjidakis DJ, Androulakis, II. Bone remodeling. *Ann N Y Acad Sci.* 2006;1092:385-396.

38. Kenkre JS, Bassett J. The bone remodelling cycle. *Ann Clin Biochem.* 2018;55(3):308-327.

39. Marques EA, Wanderley F, Machado L, et al. Effects of resistance and aerobic exercise on physical function, bone mineral density, OPG and RANKL in older women. *Exp Gerontol.* 2011;46(7):524-532.

40. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA. Exercise and bone mass in adults. *Sports medicine (Auckland, NZ).* 2009;39(6):439-468.

41. Gomez-Cabello A, Ara I, Gonzalez-Aguero A, Casajus JA, Vicente-Rodriguez G. Effects of training on bone mass in older adults: a systematic review. *Sports medicine (Auckland, NZ).* 2012;42(4):301-325.

42. Hesse S, Bertelt C, Jahnke MT, et al. Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients. *Stroke.* 1995;26(6):976-981.

43. Cho DY, Park SW, Lee MJ, Park DS, Kim EJ. Effects of robot-assisted gait training on the balance and gait of chronic stroke patients: focus on dependent ambulators. *Journal of physical therapy science.* 2015;27(10):3053-3057.

44. Pandian S, Arya KN, Kumar D. Does motor training of the nonparetic side influences balance and function in chronic stroke? A pilot RCT. *ScientificWorldJournal.* 2014;2014:769726.

45. Hessam M, Salehi R, Yazdi MJS, Negahban H, Rafie S, Mehravar M. Relationship between functional balance and walking ability in individuals with chronic stroke. *Journal of physical therapy science.* 2018;30(8):993-996.

46. Swinnen E, Beckwee D, Meeusen R, Baeyens JP, Kerckhofs E. Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. *Topics in stroke rehabilitation.* 2014;21(2):87-100.

47. Braun T, Marks D, Thiel C, Zietz D, Zutter D, Gruneberg C. Effects of additional, dynamic supported standing practice on functional recovery in patients with sub-acute stroke: a randomized pilot and feasibility trial. *Clinical rehabilitation.* 2016;30(4):374-382.

48. Berger CE, Kroner A, Stiegler H, Leitha T, Engel A. Elevated levels of serum type I collagen C-telopeptide in patients with rapidly destructive osteoarthritis of the hip. *Int Orthop.* 2005;29(1):1-5.

49. McCormick RK. Osteoporosis: integrating biomarkers and other diagnostic correlates into the management of bone fragility. *Altern Med Rev.* 2007;12(2):113-145.

50. Starup-Linde J, Vestergaard P. Biochemical bone turnover markers in diabetes mellitus - A systematic review. *Bone.* 2016;82:69-78.

51. Myint PK, Poole KE, Warburton EA. Hip fractures after stroke and their prevention. *QJM.* 2007;100(9):539-545.

52. Wheater G, Elshahaly M, Tuck SP, Datta HK, van Laar JM. The clinical utility of bone marker measurements in osteoporosis. *J Transl Med.* 2013;11:201.

Chapter 6: Summary of findings and conclusion

Summary of findings

The results presented in this dissertation demonstrated that our intervention, a low intensity aerobic walking exercise using a treadmill, body weight support system, and lower limb assistive walking device, was feasible and safe in non-ambulatory stroke survivors. In addition, after the intervention our participants showed improvement in pulmonary function shown by increases in vital capacity (VC) and forced vital capacity (FVC), cardiovascular health shown by decreases in glycated hemoglobin (HbA1c) levels, resting heart rate (rHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and bone health shown by an increase in osteocalcin (OC), a bone formation marker.

Our intervention affects the secondary outcome measures positively since it reduced depression as evidenced by decreased Patient Health Questionnaire-9 (PHQ-9) scores, and our intervention improved walking ability as judged by increased functional ambulation category (FAC) score and balance based on increased Berg Balance Scale (BBS) score. Although we did not measure the fitness level directly, increasing the means of duration of walking exercise and the speed of treadmill, and reducing the mean of percentage of body weight support imply an improvement in fitness level.

In chapter one, we introduced the health sequelae after stroke focusing on decline in cardiovascular, pulmonary, and bone health. Then we reviewed the pharmacological and non-pharmacological (such as aerobic exercise) interventions for stroke survivors in general. We explained the significance of this dissertation project and listed specific aims and hypotheses.

In chapter two, we focused on non-ambulatory stroke survivors by reviewing the health benefits of aerobic walking exercise on pulmonary, cardiovascular, and bone health in non-ambulatory stroke survivors. Only seven studies in the literature reported cardiovascular measures after aerobic exercise programs in non-ambulatory stroke survivors. No study has investigated the effect of aerobic exercise on pulmonary function or bone health in non-ambulatory stroke survivors. We summarized the health issues in the cardiopulmonary and skeletal systems and the current state of clinical research findings of aerobic walking exercise in non-ambulatory stroke survivors. We reviewed the aerobic exercise guidelines for non-ambulatory stroke survivors. Then, we reviewed the relevance of exercise position (standing vs. sitting) in terms of its potential effect in improving or maintaining the health of cardiopulmonary and bone systems in non-ambulatory stroke survivors. We briefly reviewed the development of walking assistive devices that makes walking exercise feasible for non-ambulatory stroke survivors.

In chapter three, we examined the feasibility and the effect of 8-week aerobic walking exercise on lung function in non-ambulatory stroke survivors using a treadmill, body weight support system, and gait training device. Nine non-ambulatory chronic stroke survivors completed the walking exercise, and pulmonary function test was conducted on eight of them. We showed that 8 weeks of aerobic walking exercise was feasible. Among the nine participants who completed the intervention, the compliance rate was 100%. Overall, the attrition rate was 10%. There were significant differences between pre- and post -intervention assessments in FVC ($p= 0.09$), percentage of predicted VC ($p= 0.08$), and percentage of predicted FVC ($p= 0.08$). The results are promising and suggest that the low intensity aerobic walking exercise may improve lung function. However, more studies are needed.

In chapter four, we examined the effect of low intensity aerobic walking exercise on cardiovascular risk factors in non-ambulatory stroke survivors. Nine non-ambulatory stroke survivors completed the intervention and assessment of cardiovascular function. Significant changes in HbA1c, rHR, SBP, DBP, and PHQ-9 were observed after the intervention. In addition, body weight, body mass index, and the percentage of the body weight support decreased significantly while the duration of walking exercise and treadmill speed were increased significantly after the intervention. The results in this chapter suggest that the aerobic walking exercise may improve cardiovascular function and fitness level in non-ambulatory stroke survivors.

In chapter five, we examined the effect of aerobic walking exercise on bone health in non-ambulatory stroke survivors. Nine non-ambulatory stroke survivors completed the aerobic walking exercise program. OC increased significantly from 8.51±2.28 ng/ml to 9.39±2.97 ng/ml ($p < 0.1$). ICTP increased significantly from 4.45±2.58 ng/ml to 5.31±2.92 ng/ml ($p < 0.1$). The results suggest that the low intensity aerobic walking exercise may improve bone health by increasing bone formation as judged by the respective markers. However, the low intensity aerobic walking exercise may initiate the bone remodeling process slowly, which might be due to the initial severe disability of the participants and the nature of the aerobic walking exercise. FAC and BBS were increased significantly from 1±0.0 and 7.22±10.02 to 1.33± 0.5 and 15.78±14.81, respectively.

Limitations

The sample size in this dissertation research was small and might hinder the power to detect significant changes in some of our proposed variables. This project was a pilot project. We hope that the information from this dissertation project can be used in designing future clinical studies. In addition, this dissertation project included a single intervention group without a control group, which might be a risk for bias.

We did not control for potential influences of important covariates including age, gender, ethnicity, genetics, comorbidities, medications, time since stroke, type of stroke, fitness level, sex hormones, and diet. We did not have a long term follow up assessment to investigate the long-term effect of low intensity aerobic walking exercise in non-ambulatory stroke survivors.

Since we have a small sample size, nonparametric statistical methods are preferred. However, the results were similar when we utilized Wilcoxon signed rank test (nonparametric) and paired t-test (parametric).

Future directions

A randomized control trial with single blinding of assessors, a longer intervention duration, and a long-term follow up assessment are needed to investigate the effect of the low intensity aerobic walking exercise using treadmill, body weight support system, and walking assistive device on pulmonary function, cardiovascular health, and bone health in non-ambulatory stroke survivors. Furthermore, using a multi-center trial design may help to overcome the difficulty in recruiting non-ambulatory stroke survivors for the trial.

Future trials may need to examine the influence of covariates including age, gender, ethnicity, genetics, comorbidities, medications, time since stroke, type of stroke, fitness level, sex hormones, and diet, which may affect pulmonary function, cardiovascular system, and bone health.

Furthermore, future studies may include additional cardiovascular measurements such as left ventricular function and peripheral and central blood flow. It would be interesting and important to examine whether the low intensity aerobic walking exercise could affect those measurements in non-ambulatory stroke survivors. In addition, a comparative trial to compare the effect of the low intensity aerobic walking exercise to that of the standing several times a day on cardiovascular risk factors and bone health in non-ambulatory stroke survivors.

Recruiting non-ambulatory stroke survivors into the study was a challenge task in our study. The lack of transportation and family support were the major barriers for enrollment. Future studies may enhance the enrollment effort by providing transportation to study participants or providing the intervention in nursing home or other facilities where non-ambulatory stroke survivors may live in or nearby.

Conclusion

The findings of this dissertation project prove the feasibility and safety of conducting the low intensity aerobic walking exercise for non-ambulatory stroke survivors. In addition, pulmonary function, cardiovascular health, and bone health showed promising improvements in non-ambulatory stroke survivors after the low intensity aerobic walking exercise. Future studies might utilize the data from this pilot project to design randomized control trials to better understand the effect of low intensity aerobic walking exercise on pulmonary function, cardiovascular health, and bone health in non-ambulatory stroke survivors. Future studies could also utilize different aerobic walking exercise intensities and/or durations. Future studies are needed to create guidelines for an optimal aerobic exercise program with specific details about type, intensity, duration, and frequency of exercise.