

Hypothesis

Lactate threshold-based functional training for neurocognitive and physical outcomes in elderly with type 3 diabetes: Study protocol for a long-term RCT

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Abstract

Type 3 diabetes (T3D), defined by the concurrence of type 2 diabetes and age-related cognitive impairment, is linked to progressive deterioration in both cognitive and physical function. Emerging evidence suggests that functional exercise training prescribed in relation to individualized lactate thresholds may enhance neurocognitive and physical adaptations by matching exercise intensity to individual metabolic capacity and systemic organ cross-talk. Randomized controlled trial will examine the effects of long-term, lactate-threshold-based functional training on cognitive and physical function in older adults with T3D, highlighting the role of exercise intensity in optimizing outcomes. Sixty-six adults aged 60–80 years with Type 3 diabetes and cognitive impairment, assessed by the Mini-Mental State Examination, will be recruited from the Chaharmahal and Bakhtiari Diabetes Association and randomly assigned to three groups. The intervention group will undertake a six-month, individualized high-intensity functional training program combining supervised and home-based sessions. Primary outcomes include changes in cognitive performance and physical function assessed using validated and standardized measures. It is hypothesized that lactate-threshold-guided functional exercise at tailored intensities will lead to significant improvements in both cognitive and physical function, emphasizing the critical role of exercise intensity in modulating neurocognitive and functional adaptations in elderly individuals with type 3 diabetes. This study aims to provide robust evidence for intensity-specific, lactate-threshold-based exercise prescriptions in this population.

Key Words: Type 3 diabetes, Elderly, Cognitive impairment, Lactate-threshold, Neuro-functional training

Introduction

T3D is a conceptual framework that links peripheral metabolic dysfunction to neurodegenerative changes resembling AD. In T3D, insulin resistance within the brain impairs neuronal glucose uptake and energy metabolism, leading to synaptic dysfunction and cognitive decline, which occur in parallel with classical AD pathology such as amyloid β accumulation and tau hyperphosphorylation (De la Monte & Wands, 2008). The concept of “Type 3 diabetes” has emerged to underscore the role of disrupted brain insulin signaling within the broader framework of organ crosstalk in metabolic disease. From an exercise–organ crosstalk perspective, impaired cerebral insulin action and associated metabolic dysregulation are viewed as integral components of the pathological communication between peripheral metabolic organs and the brain, contributing to cognitive impairment in individuals with type 2 diabetes. This paradigm positions the brain as an active participant in systemic insulin resistance rather than a passive recipient of peripheral metabolic dysfunction (Mittal, Mani, & Katare, 2016). Epidemiological evidence supports this linkage, with T2D patients exhibiting a substantially increased risk of dementia and cognitive decline compared to the general population (Luchsinger, 2010). The physiological characteristics of T3D, such as extracellular amyloid plaques, intracellular neurofibrillary tangles, loss of hippocampus neurons, and decreased acetylcholine production, result in reduced glucose utilization in the cerebral cortex and hippocampus (along with impaired memory and learning) (Fukuyama et al., 1994). All of these changes in the brain are brought on by long-term, uncontrolled insulin signaling and glucose metabolism (Correia et al., 2012). T3D causes a substantial decrease in glucose metabolism, especially in areas linked to memory and learning (Reiman et al., 2004). Furthermore, metabolic disturbances such as hyperglycaemia and oxidative stress contribute to neuronal dysfunction and synaptic loss, exacerbating neurode-

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-generative processes in this population. Despite these mechanistic insights, interventional strategies that effectively target both metabolic and neurocognitive dysfunction in T3D are limited.

Alongside conventional pharmacological interventions, exercise training is recognized as an effective, safe, and practical approach for managing disorders associated with type 3 diabetes. Exercise has been shown to improve glucose metabolism and insulin signalling (Flack et al., 2011), reduce inflammation (Hopps, Canino, & Caimi, 2011; Perry et al., 2016), and ameliorate cognitive impairments (Hopps et al., 2011; Perry et al., 2016). Beyond these systemic effects, exercise has pronounced benefits for brain health, including enhanced neuroplasticity and cognitive function, partly mediated through exercise induced molecular signals such as brain derived neurotrophic factor (BDNF). Importantly, exercise intensity appears to be a key modulator of these neurobiological pathways (Gordon, Benson, Bird, & Fraser, 2009; Irvine & Taylor, 2009). Lactate, a metabolite generated in greater quantities at higher exercise intensities, functions as a signalling molecule that can cross the blood-brain barrier and influence BDNF expression and associated neuroprotective pathways (Brooks, 2020). Peripheral lactate increases following intense and lactate threshold-based exercise have been linked to upregulated neurotrophic signalling within the hippocampus and cortex, regions crucial for learning and memory (Monticone, Ambrosini, Laurini, Rocca, & Foti, 2015; Smaili et al., 2018).

The LT represents the exercise intensity at which lactate production begins to exceed clearance, serving as a physiological marker of metabolic stress and substrate utilization (Brooks, 2020). Training at or above an individual's LT can amplify lactate production, thereby potentially enhancing its neurometabolic signalling effects and promoting greater neuroplastic adaptations. Evidence from animal and human studies suggests that sustained higher intensity exercise that elevates lactate levels is associated with greater neurotrophic responses compared to moderate intensity alone, although this relationship requires further clarification in clinical populations, particularly those with combined metabolic and cognitive impairments (Kumar, Sahu, Jawaid, Jayasingh Chellammal, & Upadhyay, 2025).

Despite compelling mechanistic evidence, there remains a significant gap in understanding the long term effects of lactate threshold-based functional training on cognitive, metabolic, and neuroimmune outcomes in elderly individuals with T3D. Most intervention studies in this area have focused on moderate inten-

-sity exercise or have not systematically incorporated individualized intensity prescriptions based on metabolic thresholds. As a result, it is unclear whether tailoring exercise intensity to individual lactate thresholds can optimize neurocognitive outcomes and influence metabolic-neuroimmune interactions in this high risk population. Therefore, this study protocol outlines a 6 month randomized controlled trial designed to evaluate whether individualized, lactate threshold-guided functional training enhances cognitive performance, physical function, and biomarkers of metabolic and immune regulation in elderly individuals with T3D. By integrating metabolic physiology with neurocognitive targets, this trial seeks to generate robust evidence for intensity specific exercise prescriptions as a therapeutic strategy for mitigating cognitive decline in metabolic neurodegenerative conditions.

Material and methods

Study design

This study is a multi-arm, parallel group randomized controlled trial (RCT) protocol designed to examine the effects of a long term, lactate threshold-based neuro functional training intervention on cognitive performance, physical function, metabolic markers, and systemic inflammation in older adults with T3D. Consistent with best practices for clinical exercise trials, the study design follows SPIRIT guidelines and will be reported according to CONSORT standards to ensure transparency and reproducibility. The primary aim is to determine whether a 6-month functional training program prescribed relative to lactate thresholds elicits superior improvements in cognitive, physical, and inflammatory outcomes compared with lower intensity training and usual care. Outcomes will be assessed at baseline, mid intervention (3 months), and post intervention (6 months), consistent with high quality exercise RCT protocols in the literature. The trial is registered at the Iranian Registry of Clinical Trials (IRCT20230502058055N2; Trial ID: 84611; registration date: 2025 08 07).

Participants

Community dwelling older adults aged 60–80 years with physician confirmed T2D for at least five years and evidence of mild cognitive impairment based on standardized cognitive screening tools will be recruited from the Chahar Mahal and Bakhtiari province with support from regional diabetes associations. The initial interview will include gathering information such as a medical history, describing the benefits and advantages, as well as the framework of the research project for the patient, and assessing the patient's willingness to participate in such a research project.

After this stage, based on the research entry and exit criteria and

the sample size obtained from the G-power software; 66 people will be selected as subjects in this study. In addition to the exclusion criteria, during the training sessions, if the patient does not attend three consecutive training sessions for any reason, they will be excluded from the study.

T3D is operationally defined as the co-existence of T2D and mild cognitive impairment (MCI), in the absence of dementia or other major neurological disorders.

Inclusion Criteria:

- T2D diagnosis \geq 5 years.
- Mild cognitive impairment confirmed by validated instruments.
- Ability to ambulate independently with or without assistive devices.
- Medical clearance for moderate to high intensity exercise.

Exclusion criteria:

- Clinical diagnosis of Alzheimer's disease or other neurodegenerative disorders.
- Severe cardiovascular, musculoskeletal, or neurological conditions precluding exercise.
- Uncontrolled hypertension or recent acute cardiovascular events.
- Engagement in structured exercise programs within 6 months prior to enrolment.

Sample size and randomization

A total of 66 participants will be randomized (1:1:1) into three study arms using computer generated allocation sequences, with concealment ensured by an independent statistician. The three groups are:

1. FTALT (Functional training above lactate thresholds). Subjects in this group will performed functional training at an intensity above lactate threshold (75–85% of heart rate reserve (HRR), equivalent to 80–85% of maximal oxygen uptake, equivalent to 120–125% of lactate threshold) (Belman & Gaesser, 1991; Córdova, Silva, Moraes, Simões, & Nóbrega, 2009; Ghahfarrokhi et al., 2024; Panton et al., 1996). Subjects first underwent a 4-week introductory training course (three sessions per week) under direct supervision to gain information about functional training and the gym environment, and to become familiar with the equipment (Table 2).
2. FTBLT (Functional training below lactate thresholds) Subjects in this group will performe functional training at an intensity below lactate threshold (35–45% HRR, equivalent to 50–60% maximal

oxygen uptake, equivalent to 70–75% lactate threshold) (Belman & Gaesser, 1991; Córdova et al., 2009; Ghahfarrokhi et al., 2024; Panton et al., 1996) (Table 2).

3. Control: Standard care with physical activity recommendations only.

Randomization and allocation procedures follow protocols used in comparable exercise RCTs investigating intensity specific effects on cognitive outcomes and physiological markers.

Intervention

Participants in the functional training group will initially train for four weeks, going to three sessions each week, while being closely monitored by the trainers at the sports facility. In other words, a four weeks' feasibility period with supervision will be conducted and then they will enter the main 6-month training phase. They will continue a 6-month, three-session-per-week, home-based functional training program under the guidance of a trainer after completing the required training. Every session will last 60 minutes and include the following activities: range-of-motion exercises and a low-intensity warm-up Exercises for posture maintenance, balance and sensory integration, and upper and lower body strength Cool-down and exercises for core stability, control, and pelvis. The basic recommendations for exercise prescription for older persons with type 2 diabetes (Gholizade et al., 2022; Motl, Sandroff, et al., 2017; Taylor, Barnes, & Johnson, 2022; Zhao et al., 2022) served as the basis for the formulation of this exercise regimen. Participants will get exercises in the form of video clips. The Borg scale will be used to gauge how hard the workouts are. For instance, on the Borg scale, the activities in weeks one through twelve will be 4-8 in intensity. On the Borg scale, the exercise intensity will range from 8 to 13 throughout weeks 12 through 24. By adjusting the number of repetitions and sets, the trainer can adjust the exercise's intensity throughout this time dependent on the participant's performance. Since several studies (Gaskill, Skinner, & Quindry, 2023; Hui & Chan, 2006; Irving et al., 2006) have examined the relationship between heart rate reserve (HRR), rate of perceived exertion (RPE), and lactate threshold, and concluded that there is a significant scientific relationship between these three intensity factors for measuring exercise intensity. In this study, we will therefore use heart rate reserve and the Borg scale of perceived exertion to examine the exercise intensity of the neurofunctional training group above and below the lactate threshold (The Borg scale will be used as a secondary assessment of exercise intensity).

Phases of training

Familiarization phase (2 sessions): Under the supervision of a trainer and exercise physiology specialist, they will be familiarized

with the exercises and how to perform them, and possible errors in the exercise protocol will be identified and corrected.

Supervised training (Weeks 1–4): You will be supervised by a trainer and exercise physiologist in the exercise physiology lab, who will ensure proper technique, safety, and adherence to lactate threshold-based intensity goals.

Home based training (Months 2–6): Participants will continue FT at home using structured video guidance and written protocols, with weekly remote supervision (video call) and biweekly phone checks. Exercise logs will be reviewed weekly to monitor adherence and progression

Exercise prescription and intensity titration

Participants will continue functional training under the supervision of athletic trainers for 24 weeks (three sessions per week). Each FTALT session will be consisted of 30 to 35 minutes of activity, which included 1- endurance exercises (6 min walk), 2- upper and lower body strength (hang grip, up and sit), 3- balance (tendem balance) and posture exercises, and 4- hip joint control and core stability exercises. The rest-activity ratio in this group will be 1:1 (Table 2).

Intensity is prescribed relative to lactate thresholds, operationalized through a combination of HRR, maximal oxygen uptake and perceived exertion (Borg RPE scale). Participants in FTALT will train at intensities above their LT, whereas FTBLT will train below LT. Lactate threshold determination will be established during baseline testing using standardized exercise protocols to ensure metabolic specificity.

Outcome measures

Primary outcomes

Cognitive outcomes: Processing speed (SDMT), learning (CVLT), and memory (BVRT). Multiple and intermittent tests and scales examine and evaluate different aspects of cognitive function in diabetic patients, including cognitive tests related to SDMT, CVLT and BVRT.

Physical function: In the present study, the Tendem test suite will be used to measure static and dynamic balance (Mercan, Kara, Tiftikcioglu, Mercan, & Sertpoyraz, 2016). Lower limb mobility will be measured using the Six-Step Foot Striking Test (SSST) (Nieuwenhuis, Van Tongeren, Sørensen, & Ravnborg, 2006). Walking endurance will be measured by the six-minute walk test (6MWT) and walking speed by the 10-meter walk test (10MWT) and 25-foot walk test (T25FWT) (Faramarzi et al., 2020). Agility will be measured using the timed get up and go (TUG) test (Motl, Cohen, et al., 2017). Lower body and upper body strength will be measured by the five-time chair sit-to-stand test (5TSTS), respectively (Melo et al., 2019), and handgrip will be measured (Banitalebi et al., 2020).

Secondary outcomes

- Metabolic markers: Will be measured fasting glucose, insulin, HbA1c, HOMA IR through blood samples.

Inflammatory Indices: Blood samples will be taken 48 hours before the start of the protocol and 48 hours after the last training session. Then, systemic inflammation indices including neutrophils, lymphocytes and platelets will be measured. Then, systemic inflammation indices (neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and systemic inflammation index) will be calculated using the following formulas (Ghahfarrokhi, Banitalebi, Faramarzi, & Motl, 2022).

neutrophil to lymphocyte ratio (NLR)= neutrophil / lymphocyte

platelet to lymphocyte ratio (PLR)= platelet / lymphocyte

Systemic immune-inflammation index (SII)= (neutrophil × platelet)/ lymphocyte

- Anthropometric measurements: include height, weight, body mass index, body fat percentage, and muscle percentage. For this purpose, height will be measured using a wall-mounted height scale and barefoot, and weight will be measured using a digital scale and minimal clothing. Body mass index will be calculated using the formula body mass index (weight (in kilograms) / height squared (meters)).

- Quality of life and descriptive indicators via validated questionnaires. Assessments occur at baseline, 3 months, and 6 months, consistent with rigorous exercise intervention protocols.

Safety and monitoring

Participant safety and risk mitigation will be monitored through standardized functional screenings, careful intensity progression, and documentation of adverse events. Assessors conducting outcome measurements will remain blinded to group allocation to minimize detection bias (Table 1).

Table 1. Summary of process evaluation methods.

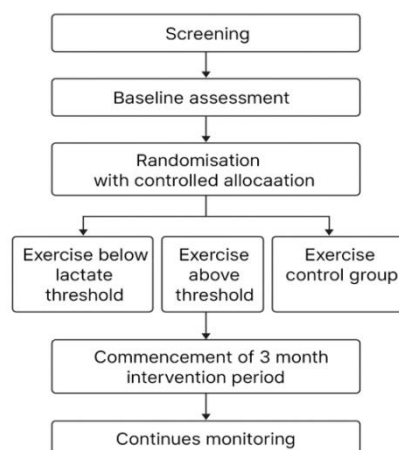


Table 2. Details of the six-month functional training protocol

Microcycles	Sessions	Sessions of comprehensive home-based neurofunctional training (CHBNFT)	Target
Practice phase (four weeks)	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 2-3 (i.e., fairly light-moderate)	1- Breathing exercises (Breathe in (5s) and out (5s), 2 × 2 min).	Warm-up and increasing range of motion.
		2- Marching in place (2×60s).	
		3- Stretch exercise: Lying knee bend, Knee roll, Sideways lean, table slide, chair Lunge stretch, seated shoulder flexion, seated shoulder abduction, seated shoulder rotation, seated hip abduction & adduction stretches, Cross-Legged Seated Torso (increase stretch as tolerated, 10s/2 reps, circle training)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Semi-tandem stand exercise: Subjects stand on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 20s with eyes open, arms crossed over the chest, and bare feet (2 sets, 2 min rest between sets).	Balance training and sensory integration
		2- Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 10 s with eyes open, arms crossed over the chest, and bare feet (2 sets, 2 min rest between sets).	
		3- Long step: the patient must walk performing long steps on firm floor (at least 40-50 cm long) using some signs on the floor as a guide) (30s, 2 reps)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	4- 8-foot get-up-and-go (2 reps, 2 min rest between reps).	Posture exercises
		5- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (2 sets, 8 reps each foot)	
		6- Six Spot Step Exercise (2 times)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (2 sets, 8 reps)	Posture exercises
		2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (2 sets, 8 reps).	
		3- Excessive trunk flexion (2 sets, 10 reps).	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Partial squats (Reps until moderate fatigue). (2 sets, 8 reps).	Increase upper and lower-extremity strength
		2- Stationary Lunge (Reps until moderate fatigue) (2 sets, 8 reps).	
		3- Forearm rotation (Reps until moderate fatigue) (2 sets, 8 reps).	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	4- Hand climb (Reps until moderate fatigue) (2 sets, 8 reps).	Pelvic control exercises and core stability training
		5- Modified Push-Up. (2 sets, 8 reps).	
		6- 30-second sit-stand (2 sets, 8 reps).	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	7- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially.	Pelvic control exercises and core stability training
		1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek, Hump and hollow and Sit hip hitch (2 sets, 8 reps).	
		2- Cat/camel, Dead bug, Side bridging, Birdog exercises, Hip abduction and Bridge exercises (2 sets, 8 reps).	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Breathing exercises (Breathe in (5s) and out (5s), 2 × 2 min).	Warm-up and increasing range of motion.
		2- Marching in place (2×60s).	
		3- Stretch exercise: Lying knee bend, Knee roll, Sideways lean, table slide, chair Lunge stretch, seated shoulder flexion, seated shoulder abduction, seated shoulder rotation, seated hip abduction & adduction stretches, Cross-Legged Seated Torso (increase stretch as tolerated, 10s/2 reps, circle training)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Semi-tandem stand exercises: Subjects stand on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 30 s with eyes open, arms crossed over the chest, and bare feet (2 sets, 2 min rest between sets).	Balance training and sensory integration
		2- Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 10 s with eyes open, arms crossed over the chest, and bare feet (2 sets, 2 min rest between sets).	
		3- Long step: the patient must walk performing long steps on firm floor (at least 40-50 cm long) using some signs on the floor as a guide) (30s, 2 reps, 2 min rest between sets)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	4- 8-foot get-up-and-go (2 reps, 2 min rest between reps).	Posture exercises
		5- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (2 sets, 8 reps each foot, 2 min rest between sets)	
		6- Six Spot Step Exercise (2 times)	
1-4	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift	Posture exercises

Table 2. Continue

		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (2 sets, 8 reps, 2 min rest between sets)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (2 sets, 8 reps, 2 min rest between sets).</p> <p>3- Excessive trunk flexion (2 sets, 10 reps, 2 min rest between sets).</p>	Posture exercises
		<p>1- Partial squats (Reps until moderate fatigue) (2 sets, 2 min rest between sets).</p> <p>2- Stationary Lunge (Reps until moderate fatigue) (2 sets, 8 reps).</p> <p>3- Forearm rotation (Reps until moderate fatigue) (2 sets, 8 reps, 2 min rest between sets).</p> <p>4- Hand climb (Reps until moderate fatigue) (2 sets, 8 reps, 2 min rest between sets).</p> <p>5- Modified Push-Up. (2 sets, 8 reps, 2 min rest between sets).</p> <p>6- 30-second sit-stand (2 sets, 8 reps, 2 min rest between sets).</p> <p>7- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially.</p>	Increase upper and lower-extremity strength
		<p>1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek, Hump and hollow and Sit hip hitch (2 sets, 8 reps, 2 min rest between sets).</p> <p>2- Cat/camel, Dead bug, Side bridging, Birdog exercises, Hip abduction and Bridge exercises (2 sets, 8 reps, 2 min rest between sets).</p>	Pelvic control exercises and core stability training
5-8	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	<p>1- Breathing exercises (Breathe in (5s) and out (10s), 2x2 min, 1 min rest between reps).</p> <p>2- Marching in place (90s).</p> <p>3- Stretch exercise: lying shoulder flexion, lying shoulder abduction, lying shoulder rotation, lying hip abduction & adduction stretches and Chair calf stretch (Hold stretches 30s with mild tension and minimal discomfort).</p>	Warm-up and increasing range of motion.
		<p>1- Semi-tandem stand exercises: Subjects stand on a firm surface in semi-tandem (60s)</p> <p>2- Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 30 s with eyes open, arms crossed over the chest, and bare feet.</p> <p>2- Long step (the patient must walk performing long steps (at least 40-50 cm long) using some signs on the floor as a guide) (30s)</p> <p>3- 8-foot get-up-and-go(1rep).</p> <p>4- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (2 sets, 12 reps each foot)</p> <p>5- Six Spot Step Exercise (3 times, 2 min rest between sets)</p>	Balance training and sensory integration
		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (12 reps)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (10 reps).</p> <p>3- Excessive trunk flexion (12 reps).</p>	Posture exercises
		<p>1- Partial squats (Reps until moderate fatigue) (12 reps).</p> <p>2- Hand climb (Reps until moderate fatigue) (12 reps).</p> <p>3- Stationary Lunge (Reps until moderate fatigue) (12 reps).</p> <p>4- Modified Push-Up. (12 reps).</p> <p>5- 30-second sit-stand (2 reps, 2 min rest between sets).</p> <p>7- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially.</p>	Increase upper and lower-extremity strength
		<p>1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek (12 reps).</p> <p>2- Cat/camel, Dead bug, Side bridging (flexed knee), Birdog exercise, Hip abduction and Bridge exercise (12 reps).</p>	Pelvic control exercises and core stability training
9-12	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 4-6 (i.e., Somewhat hard -Hard)	<p>1- Pursed Lips Breathing (Breathe in (5s) and out (10s), 2x2 min, 1 min rest between reps).</p> <p>2- Marching in place (2 x 60s, 2 min rest between sets).</p> <p>3- Stretch exercise: lying shoulder flexion, lying shoulder abduction, lying shoulder rotation, lying hip abduction & adduction stretches and Chair calf stretch (Hold stretches 45s with mild tension and minimal discomfort).</p>	Warm-up and increasing range of motion.

Table 2. Continue

		<p>1- Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 60 s with eyes open, arms crossed over the chest, and bare feet.</p> <p>2- Long step (the patient must walk performing long steps (at least 40-50 cm long) using some signs on the floor as a guide) (45s)</p> <p>3- 8-foot get-up-and-go (2 reps, 2 min rest between reps).</p> <p>4- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (2 sets, 15 reps each foot)</p> <p>5- Six Spot Step Exercise (4 times, 2 min rest between sets)</p>	Balance training and sensory integration
		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (15 reps)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (15 reps).</p> <p>3- Excessive trunk flexion (15 reps).</p>	Posture exercises
		<p>1- Partial squats (Reps until moderate fatigue) (15 reps).</p> <p>2- Hand climb (Reps until moderate fatigue) (15 reps).</p> <p>3- Stationary Lunge (Reps until moderate fatigue) (15 reps).</p> <p>4- Modified Push-Up. (15 reps).</p> <p>5- 30-second sit-stand (3 reps, 2 min rest between sets).</p> <p>6- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially.</p>	Increase upper and lower-extremity strength
		<p>1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek (15 reps).</p> <p>2- Cat/camel, Dead bug, Side bridging (flexed knee), Birdog exercise, Hip abduction and Bridge exercise (15 reps).</p>	Pelvic control exercises and core stability training
13-16	<p>S1, S2 and S3 (60 min)</p> <p>Rating of Perceived Exertion (RPE; of 6-8 (i.e., Somewhat hard -Hard)</p>	<p>1- Pursed Lips Breathing (Breathe in (5s) and out (10s), 2×3 min, 1 min rest between reps).</p> <p>2- Marching in place (2 × 2min, 2 min rest between sets).</p> <p>3- Stretch exercise: lying shoulder flexion, lying shoulder abduction, lying shoulder rotation, lying hip abduction & adduction stretches and Chair calf stretch (Hold stretches 60s with mild tension and minimal discomfort).</p>	Warm-up and increasing range of motion.
		<p>1- 1- Semi-tandem stand exercise: Subjects stand on a soft floor in semi-tandem Romberg stance (heel-to-toe) for 20s with eyes open, arms crossed over the chest, and bare feet (2 sets, 2 min rest between sets).</p> <p>2-Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 2×120s with eyes open, arms crossed over the chest, and bare feet.</p> <p>2- Long step (the patient must walk performing long steps (at least 40-50 cm long) using some signs on the floor as a guide) (60s)</p> <p>3- 8-foot get-up-and-go (3 reps, 2 min rest between sets).</p> <p>4- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (3 sets, 15 reps each foot)</p> <p>5- Six Spot Step Exercise (4 times, 2 min rest between sets)</p>	Balance training and sensory integration
		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (20 reps)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (15 reps).</p> <p>3- Excessive trunk flexion (20 reps).</p>	Posture exercises
		<p>1- Partial squats (Reps until moderate fatigue) (20 reps).</p> <p>2- Hand climb (Reps until moderate fatigue) (20 reps).</p> <p>3- Stationary Lunge (Reps until moderate fatigue) (20 reps).</p> <p>4- Modified Push-Up. (20 reps).</p> <p>5- 30-second sit-stand (4 rep).</p> <p>6- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on bench or chair (20 reps).</p>	Increase upper and lower-extremity strength
		<p>1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek (20 reps).</p> <p>2- Cat/camel, Dead bug, Side bridging (flexed knee), Birdog exercise, Hip abduction and Bridge exercise (20 reps).</p>	Pelvic control exercises and core stability training

Table 2. Continue

17-20	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 6-8 (i.e., Somewhat hard -Hard)	<p>1- Marching in place (2 × 3min, 2 min rest between sets).</p> <p>2- Stretch exercise: lying shoulder flexion, lying shoulder abduction, lying shoulder rotation, lying hip abduction & adduction stretches and Chair calf stretch (Hold stretches 2×60s with mild tension and minimal discomfort, 2 min rest between sets).</p>	Warm-up and increasing range of motion.
		<p>1- Semi-tandem stand exercise: Subjects stand on a soft floor in semi-tandem Romberg stance (heel-to-toe) for 2×15s with eyes close, arms crossed over the chest, and bare feet (2 min rest between sets).</p> <p>2-Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 2×30s with eyes close, arms crossed over the chest, and bare feet (2 min rest between sets).</p> <p>2- Long step (the patient must walk performing long steps (at least 40-50 cm long) using some signs on the floor as a guide) (2 ×60s, 2 min rest between sets)</p> <p>3- 8-foot get-up-and-go (4 reps, 2 min rest between reps).</p> <p>4- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (3 sets, 15 reps each foot, 2 min rest between sets)</p> <p>5- Six Spot Step Exercise (4 times, 2 min rest between sets)</p>	Balance training and sensory integration
		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (2×15 reps, 2 min rest between sets)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (2×15 reps, 2 min rest between sets).</p> <p>3- Excessive trunk flexion (2×15 reps, 2 min rest between sets).</p>	Posture exercises
		<p>1- Partial squats (2×Reps until moderate fatigue, 2 min rest between sets)</p> <p>2- Hand climb (Reps until moderate fatigue) (2×15 reps, 2 min rest between sets).</p> <p>3- Stationary Lunge (2×Reps until moderate fatigue, 2 min rest between reps).</p> <p>4- Modified Push-Up (2×15, 2 min rest between reps).</p> <p>5- 30-second sit-stand (5 reps, 2 min rest between reps).</p> <p>6- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially (2×15, 2 min rest between reps).</p>	Increase upper and lower-extremity strength
		<p>1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek (2×15 reps, 2 min rest between reps).</p> <p>2- Cat/camel, Dead bug, Side bridging (flexed knee), Birddog exercise, Hip abduction and Bridge exercise (2×15, 2 min rest between sets).</p>	Pelvic control exercises and core stability training
21-24	S1, S2 and S3 (60 min) Rating of Perceived Exertion (RPE; of 6-8 (i.e., Somewhat hard -Hard)	<p>1- Marching in place (2 × 5 min).</p> <p>2- Stretch exercise: lying shoulder flexion, lying shoulder abduction, lying shoulder rotation, lying hip abduction & adduction stretches and Chair calf stretch (Hold stretches 2×60s with mild tension and minimal discomfort, 2 min rest between sets).</p>	Warm-up and increasing range of motion.
		<p>1- Semi-tandem stand exercise: Subjects stand on a soft floor in semi-tandem Romberg stance (heel-to-toe) for 2×20s with eyes close, arms crossed over the chest, and bare feet (2 min rest between sets).</p> <p>2-Semi-tandem walking exercises: Subjects walk on a firm floor in semi-tandem Romberg stance (heel-to-toe) for 2×60s with eyes close, arms crossed over the chest, and bare feet (2 min rest between sets).</p> <p>2- Long step (the patient must walk performing long steps (at least 40-50 cm long) using some signs on the floor as a guide) (3×60s, 2 min rest between sets)</p> <p>3- 8-foot get-up-and-go (5 reps, 2 min rest between reps).</p> <p>4- Step overs (1). Standing approximately 6 inches from a 6-inch cone, step over on one leg while maintaining balance then follow with the second leg. Step back over the cone to start and repeat 10 times. For lateral challenges, step laterally over the cone and back. Cone height can be increased for progression. (3 sets, 20 reps each foot, 2 min rest between sets)</p> <p>5- Six Spot Step Exercise (5 times, 2 min rest between sets)</p>	Balance training and sensory integration
		<p>1- Pelvic tilt sitting, Cheek to cheek, Hump and hollow, Rocking, Hip hitch, Leg lift (3×15 reps, 2 min rest between reps)</p> <p>2- Transition of posture from sitting on heels to kneeling and from kneeling to semi-kneeling, with and without trunk rotation holding a Swiss ball (2×15 reps).</p> <p>3- Excessive trunk flexion (3×15 reps, 2 min rest between reps).</p>	Posture exercises

Table 2. Continue

1- Partial squats (3×Reps until moderate fatigue, 2 min rest between reps)	Increase upper and lower-extremity strength
2- Hand climb (Reps until moderate fatigue) (3×15 reps, 2 min rest between reps).	
3- Stationary Lunge (3×Reps until moderate fatigue, 2 min rest between reps).	
4- Modified Push-Up (3×15, 2 min rest between reps).	
5- 30-second sit-stand (5 reps, 2 min rest between reps).	
6- Penny pick up (1). Walk three steps to penny on the floor, squat down or lunge with good form, pick up penny, and repeat five times. If the individual is unable to bend down and pick up the penny, it can be placed on a bench or chair initially (3×15, 2 min rest between sets).	
1- Pelvic control exercises: Knee roll, Pelvic tilt lying, Pelvic tilt sitting, Cheek to cheek (3×15 reps, 2 min rest between sets).	Pelvic control exercises and core stability training
2- Cat/camel, Dead bug, Side bridging (flexed knee), Bird dog exercise, Hip abduction and Bridge exercise (3×15, 2 min rest between sets).	

Statistical analysis

Analyses will follow intention to treat (ITT) principles. Based on ITT principle missing data will be imputed based on multiple imputation method by SPSS software. Mean and SD will use for descriptive analysis. Two-way ANOVA with group × time interactions effect will examine primary and secondary outcomes changes. Ordinarily non parametric tests will be applied when data distribution not normal. p value <0.05 will be considered statistically significant. Spss software version-25 and Grap-pad PRISM-9 will use for all statistical analysis.

Ethical considerations

The trial has received approval from the Research Ethics Committee of Shahrekord University (IR.SKU.REC.1402.032). All participants will provide written informed consent prior to study entry. This protocol adheres to ethical standards for human research and exercise interventions in clinical populations.

Discussion

This RCT will investigate how long-term neuro-functional training at different intensities affects cognition and systemic inflammation in older adults with T3D. Exercise induces systemic adaptations via myokines and exerkinases, including irisin, cathepsin B, and lactate, which promote BDNF expression and neurogenesis (Delezie et al., 2019). The present randomized controlled trial will have designed to examine the effects of long-term neuro-functional training performed at different perceived intensity levels on cognitive performance and systemic inflammatory markers in older adults with type 2 diabetes and cognitive impairment. Although exercise intensity will prescribe using perceived exertion rather than direct physiological measurements, perceived intensity remains a practical and widely accepted method for regulating exercise load in older adults (Garber et al., 2011).

Neuro-functional training is a type of exercise that includes strength, balance and coordination. This type of training uses parts of the body and helps the body adapt in a good way. It can

even help with inflammation. When older people do exercises that have different parts, like strength and balance and movement it can help reduce inflammation.

This is because these exercises can help the body use insulin better help the muscles and immune system work together and get people to move around more of sitting still. Neuro-functional training is a way to do this because it combines functional strength, balance and neuromotor elements, which is what helps the body adapt and reduce inflammation. Within an organ crosstalk framework, the observed alterations in inflammatory markers are likely to reflect the integrated metabolic and functional load imposed by the training stimulus, rather than the activation of a single isolated physiological mechanism (Xing et al., 2022).

Lactate, traditionally a metabolic byproduct, acts as a signaling molecule enhancing hippocampal plasticity and angiogenesis via HCAR1 and PGC1- α pathways (Boycott et al., 2025). Exercise also modulates low-grade systemic inflammation by reducing pro-inflammatory adipokines and increasing anti-inflammatory signaling (Whitham & Febbraio, 2016). Important information on the viability and therapeutic benefits of functional training for elderly with T3D will be provided by the findings of this planned study. It is anticipated that exercise over the lactate threshold will reduce inflammation and enhance cognitive function. The study expects to investigate the difference of six months of functional exercises above and below the lactate threshold on inflammatory, functional, and cognitive profile of patients with T3D. We will examine how exercise with different intensity differs in patients with T3D since lactate is a substrate for the brain. We expect that exercise high intensity will enhance the functional and cognitive profile of these patients. Silveria and colleagues, (2021), in a study that looked at the effects of combined exercise training on metabolic markers and cognitive functions in middle-aged and older people with T2D found that an 8-week program of combined exercise training improves cognitive functions like attention/concentration, cognitive flexibility, and inhibitory control. and helps those with T2D function better cognitively. Additionally, the combined exercise program lowers mean and

diastolic blood pressure, peripheral insulin resistance, and clinical improvements in functional areas (Silveira-Rodrigues et al., 2021). Kriwong and associates, (2021), looked at how physical-cognitive workouts affected the mental and physical functioning of older adults with T2D and balance issues. They found that combined exercise improved Activities of Daily Living (ADL) and physical fitness. However, neither the fall rate nor psychological effects were considerably improved by this exercise regimen (Kriwong, Vongsirinavarat, Rueankam, & Sumalrot, 2021). Also, Taylor et al, (2022), investigated the benefits of high-intensity interval training for improving cognitive aging in cardiac patients and concluded that cardiovascular fitness with high-intensity interval training improves cerebrovascular function and cognitive aging (Taylor et al., 2022). Xue et al, (2022), investigated the potential mechanisms of lactate in mediating exercise-enhanced cognition: a dual role as an energy source and a signaling molecule, and concluded that changes in the brain and peripheral nervous system, exercise-induced energy metabolism, may be an exercise-induced potential on the function of neurons. Brain-derived lactate and myogenic lactate are produced in greater amounts during moderate-to-intense exercise. Lactate serves as both a substrate for energy supply and a signaling molecule in the brain, which enhances cognitive performance (Xue, Liu, Hu, Bian, & Lou, 2022). The present randomized controlled trial will be designed to investigate the long-term effects of neuro-functional training performed at different exercise intensities on cognitive performance and systemic inflammation in older adults with Type 3 Diabetes (T3D). Based on existing evidence, the following hypotheses will be proposed:

1- Long-term neuro-functional training performed above the lactate threshold will lead to significantly greater improvements in cognitive functions, including attention, executive function, inhibitory control, and memory, compared with training performed below the lactate threshold in older adults with T3D.

2- Neuro-functional training above the lactate threshold will result in a greater reduction in low-grade systemic inflammatory markers compared with training below the lactate threshold.

3- Multicomponent neuro-functional training integrating strength, balance, and coordination will improve physical function and activities of daily living (ADL) in older adults with T3D, regardless of psychological outcomes.

4- Regulation of exercise intensity using perceived exertion is sufficient to elicit meaningful metabolic, inflammatory, and neurocognitive adaptations in older adults, despite the absence of direct physiological measurements of lactate threshold.

Expected mechanisms

Lactate as a Neuroactive Signaling Molecule: Lactate, traditionally considered a metabolic byproduct, is now recognized as a key signaling molecule involved in exercise-induced brain adaptations. During moderate-to-high intensity exercise, increased peripheral and central lactate production activates lactate-sensitive pathways, including the hydroxycarboxylic acid receptor 1 (HCAR1) and the PGC-1 α signaling cascade. Activation of these pathways enhances hippocampal angiogenesis, synaptic plasticity, and neurogenesis, thereby supporting cognitive improvements. These effects are expected to be more pronounced during exercise performed above the lactate threshold (Proia, Di Liegro, Schiera, Fricano, & Di Liegro, 2016).

Cerebrovascular and Metabolic Adaptations: Exercise intensities approaching or exceeding the lactate threshold are associated with improvements in cardiovascular fitness and cerebrovascular function. Enhanced cerebral blood flow and oxygen delivery may contribute to improved neuronal metabolism and cognitive performance. These vascular adaptations are particularly relevant for older adults with T3D, who often exhibit impaired cerebral perfusion and metabolic dysfunction (Bliss, Wong, Howe, & Mills, 2021).

Lactate as an Energy Substrate for the Brain: In addition to its signaling role, lactate serves as an efficient energy substrate for neurons. Exercise-induced elevations in brain-derived and muscle-derived lactate provide an alternative fuel source that may compensate for impaired glucose metabolism in individuals with diabetes. The dual role of lactate as both an energy substrate and signaling molecule is expected to underpin the cognitive benefits associated with higher-intensity functional training (Riske, Thomas, Baker, & Dursun, 2017).

Key considerations of this protocol include:

1. Structured home-based training to enhance feasibility and adherence while maintaining safety.
2. Monitoring intensity and progression to ensure therapeutic efficacy and minimize risk in older adults with metabolic-cognitive comorbidities.
3. Multi-timepoint assessment of cognitive, functional, and inflammatory outcomes allows characterization of both early and long-term adaptations.

Limitations include reliance on perceived exertion rather than direct lactate measurement during home-based sessions, and restricted inflammatory markers to hematological indices. Future research incorporating real-time lactate monitoring, broader biomarker panels, and neuroimaging may elucidate mechanisms of exercise-induced adaptations more precisely.

Conclusion

Exercise can benefit cognition in older adults and those with T2D. The lactate threshold is a key metabolic marker, and lactate may act as a signaling molecule for brain health. However, the efficacy of functional training prescribed specifically relative to the lactate threshold in T3D is unknown. This protocol describes the first long-term RCT to compare the effects of high-intensity (above LT) vs. low-intensity (below LT) neuro-functional training on cognitive and physical outcomes in elderly with T3D. It will provide novel evidence on whether tailoring exercise intensity to individual metabolic capacity optimizes outcomes.

This protocol study establishes a rigorous, mechanistically informed framework to evaluate long-term, lactate-threshold-based neuro-functional training in older adults with T3D. The study emphasizes intensity-specific exercise prescription and combines supervised and home-based sessions to optimize cognitive, functional, and inflammatory outcomes. Findings are expected to inform evidence-based guidelines for tailored exercise interventions, supporting non-pharmacological strategies to preserve cognition, enhance functional independence, and modulate systemic inflammation.

Practical applications and limitations

1) Clinical Guidance: Provides a replicable framework for physiotherapists and healthcare providers to implement intensity-tailored NFT targeting cognitive enhancement and inflammation reduction in elderly T3D patients.

2) Feasibility of Home-Based Interventions: Demonstrates the safe and progressive delivery of NFT outside clinical settings, improving adherence and engagement.

3) Non-Pharmacological Neuroprotection: High-intensity NFT above lactate threshold offers a drug-free strategy to mitigate cognitive decline and systemic inflammation.

4) Exercise Prescription Blueprint: Microcycle and macrocycle framework provides a replicable model for progressive neuromotor and functional training in older adults with metabolic-cognitive comorbidities.

5) Public Health Implications: Integration into diabetes care may reduce dementia-related healthcare burden by addressing sedentary behavior, sarcopenia, and chronic inflammation.

Limitations

1) Complete uncontrollability of the home training environment: Since neuro-functional training is performed in the home environment, it is not possible to precisely control environmental conditions such as space, light, temperature, noise, and movement safety for all participants in the same way. This can

affect the quality of the training and the physiological and movement responses of the subjects.

2) Accuracy in controlling exercise intensity relative to lactate threshold. Determining and maintaining exercise intensity above or below lactate threshold in the home environment is associated with limitations. Because it is not possible to use precise laboratory equipment (such as blood lactate analysis), and exercise intensity is often controlled based on indirect indicators such as heart rate or the perceived exertion scale (RPE), which may not be accurate enough.

What is already known on this subject?

Exercise can benefit cognition in older adults and those with T2D. The lactate threshold is a key metabolic marker, and lactate may act as a signaling molecule for brain health. However, the efficacy of functional training prescribed specifically relative to the lactate threshold in T3D is unknown.

What this study adds?

This protocol describes the first long-term RCT to compare the effects of high-intensity (above LT) vs. low-intensity (below LT) neuro-functional training on cognitive and physical outcomes in elderly with T3D. It will provide novel evidence on whether tailoring exercise intensity to individual metabolic capacity optimizes outcomes.

Acknowledgements

It is truly fitting to express gratitude and appreciation to the esteemed and wise professors, Dr. Ebrahim Bani Talebi and Dr. Mostafa Rahimi, who, with a grace as radiant as the sun, illuminated the land of the heart and enriched the garden of knowledge and learning through their effective and constructive guidance.

Funding

This research has no financial support and is not supported by any organization, and all financial costs of the research are borne by the author and the authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The trial has received approval from the Research Ethics Committee of Shahrekord University (IR.SKU.REC.1402.032).

Informed consent Performed.

Author contributions

Conceptualization: Z.R.F.; **Methodology:** M.M.G.; **Software:** E.B.; **Validation:** M.R.; **Formal analysis:** Z.R.F.; **Investigation:** E.B.; **Resources:** M.M.G.; **Data curation:** M.M.G.; **Writing - original draft:** Z.R.F.; **Writing - review & editing:** M.M.G.; **Visualization:** E.B.; **Supervision:** E.B.; **Project administration:** M.M.G.; **Funding acquisition:** Z.R.F.;

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