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Research Protocol

Physiotherapy Section

Effects of Blood Flow Restriction Training on Quadriceps Muscle Strength and Biochemical Parameters among Individuals with Type 2 Diabetes Mellitus: A Protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is characterised by poor glucose metabolism, cardiovascular complications, and musculoskeletal deterioration, which are linked to hyperglycaemia, dyslipidaemia, and sarcopenia (age-related, involuntary loss of muscle mass and strength), respectively. Blood Flow Restriction Training (BFRT) is a novel technique being used to treat various metabolic and musculoskeletal complications related to T2DM.

Need of the study: BFRT is an effective training strategy for people with physical limitations. Compared to high Resistance Training (RT), mechanical load is markedly reduced with BFRT while inducing similar gains in muscle mass and strength. The present study aims to identify a better exercise programme that provides better control of diabetes and reduces the chances of cardiovascular and musculoskeletal complications.

Aim: This study aims to investigate the effects of BFRT on quadriceps muscle strength, hyperglycaemia, and hyperlipidaemia in individuals with T2DM.

Materials and Methods: Participants in this randomised controlled trial will be recruited using criterion-based purposive sampling from the outpatient physiotherapy department of MM Super Specialty Hospital, Mullana-Ambala, Haryana, from October 2024 to March 2025. A total of 58 individuals aged 35-70 years, diagnosed with T2DM for a minimum of two years and with Glycosylated Haemoglobin (HbA1c) ≥6.5, will be included upon physician referral and randomised into two groups: an experimental group and a control group via block randomisation. The experimental group will undergo BFRT for four weeks, while the control group will undergo RT for four weeks. Pre- and post-intervention assessments will be conducted using an isokinetic dynamometer for quadriceps muscle strength, and the HbA1c and lipid profile will be evaluated for metabolic symptoms. The Kolmogorov-Smirnov test will be used to check the normality of the data. If the data are normally distributed, paired and unpaired t-tests will be used for within-group analysis and between-group analysis, respectively. If the data are not normally distributed, the Wilcoxon Signed-Rank test and Mann-Whitney test will be used for within- and between-group analyses, respectively.

Keywords: Diabetes mellitus, Glycated haemoglobin, Hyperglycaemia, Hyperlipidaemias, Quadriceps muscle

INTRODUCTION

T2DM is a chronic, non-communicable metabolic disease marked by high Blood Glucose (BG) levels due to inadequate insulin secretion from the pancreatic β-cells and reduced tissue responsiveness to insulin, resulting in hyperglycaemia [1,2]. Due to impaired insulin production, individuals with T2DM are more vulnerable to the development of dyslipidaemia and hyperglycaemia [3]. High levels of Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein (LDL), and Very Low-Density Lipoprotein (VLDL) (i.e., dyslipidaemia), as well as Glycated Haemoglobin (HbA1c), are directly or indirectly linked to a higher incidence of cardiovascular problems [4]. Hyperglycaemia may also lead to decreased strength, muscle mass, and eventually sarcopenia [5]. The American Diabetes Association (ADA) guidelines recommend maintaining HbA1c levels below seven to minimise morbidity and complications in T2DM [6]. It is proven that a reduction of approximately 0.6% in HbA1c is achieved through RT and Aerobic Exercises (AE), whereas a 1% absolute drop in HbA1c is associated with a 15%-20% reduction in major cardiovascular events and a 37% decrease in microvascular complications [6-8].

'KAATSU Training'/'adding pressure to training'/BFRT was developed by Southeast Asia Treaty Organisation (SATO) in Japan and has become one of the most novel techniques used today to increase functional strength and muscle Cross-Sectional Area (CSA) [9,10]. Based on the concept of generating peripheral vascular occlusion, Low-Load Blood Flow Restriction (LL-BFR) can significantly increase thigh and hip muscular CSA and maximise contractile strength [11]. The effects of LL-BFR on muscle hypertrophy are hypothesized to be mediated by enhanced mechano-transduction and hormonal responses, acute generation of reactive oxygen species, or cell swelling [12]. It enhances contraction-mediated Glucose Transporter 4 (GLUT4) translocation via the Ca^{2+}/CAMKII (calmodulin-dependent protein kinase) pathway and activates AMP-activated protein kinase (AMPK), promoting glucose absorption. This suggests that combining BFRT with low-resistance exercise may result in similar increases in muscle CSA and strength as high-Resistance Training (RT), which would be practical and safer, especially for elderly individuals [13]. It also exhibits hypoglycemic effects when combined with low-load exercises in persons with T2DM [14]. BFRT dramatically lowers TC and LDL levels while tending to lower TG and simultaneously raising HDL cholesterol in overweight and obese individuals, thereby reducing the incidence of cardiovascular diseases [15].

REVIEW OF LITERATURE

A randomised crossover study was previously conducted involving 10 women with T2DM. Participants were randomly assigned to one of three training conditions on three non-consecutive days: (1) low-

load exercise; (2) LL-BFR exercise; and (3) high-load exercise. Blood Glucose (BG) concentrations were measured before, immediately after, and 60 minutes following the interventions. In this trial, BFRT displayed superiority in reducing BG compared to low-load and high-load resistance exercises [14].

A randomised controlled study was conducted on middle-aged patients with T2DM to investigate the efficacy of BFR-RT in improving metabolic abnormalities, Blood Pressure (BP), obesity, and Atherosclerotic Cardiovascular Disease (ASCVD) risk. Participants were randomly assigned to three groups: a control group (n=31), a BFR-RT group (n=32), and an AE group (n=30). The control group received a health education and follow-up programme, while the AE group trained at moderate intensity for 60 minutes each session, and the BFR-RT group trained at low intensity for 40 minutes each session, three times weekly. After six months of the trial, both exercise groups (i.e., BFR-RT and AE) showed significant improvements in HbA1c and dyslipidaemia compared to the control group [16].

Another randomised controlled study was conducted on older adults with T2DM, in which 98 participants were randomly divided into three groups: the Blood Flow-restrictive Resistance Exercise (BFRE) group (n=34), moderate-intensity RT group (n=31), and the control group (n=33). The two exercise groups engaged in supervised training sessions lasting 50 minutes each, three times weekly, while the control group received education on health and lifestyle. After six months of intervention, the HbA1C levels, blood lipids, and muscle performance in the two exercise groups were significantly improved compared to the control group [17].

As more Randomised Controlled Trials (RCTs) may be needed to confirm the effects of BFRT in individuals with T2DM, this study aims to investigate the effects of BFRT on quadriceps muscle strength, hyperglycaemia, and dyslipidaemia in individuals with T2DM.

Study Objectives

Primary objectives:

- To examine the effects of BFRT on quadriceps muscle strength in individuals with T2DM.
- To assess the impact of BFRT on hyperglycaemia in individuals with T2DM.
- To compare the effects of BFRT and RT on quadriceps muscle strength and hyperglycaemia in individuals with T2DM.

Secondary objective:

- To assess the impact of BFRT on hyperlipidaemia in individuals with T2DM.

Research Hypothesis

Null hypothesis:

- BFRT will have no significant impact on quadriceps muscle strength and biochemical parameters in individuals with T2DM.

Alternate hypothesis:

- BFRT will have a significant impact on quadriceps muscle strength and biochemical parameters in individuals with T2DM.

MATERIALS AND METHODS

Participants in this RCT will be recruited via criterion-based purposive sampling from the outpatient physiotherapy department of M.M. Super Specialty Hospital, Mullana-Ambala, Haryana, from October 2024 to March 2025.

Sample size calculation: Using G Power software (version 3.1.9.7), a sample size of 52 was calculated, based on an effect size of 0.8 and a power of the study of 0.80. Taking into account a 10% dropout rate, the final sample size included in the study will be 58. Individuals will be randomised into two groups: an experimental group and a control group, using block randomisation.

Inclusion criteria: Men and women aged between 35-70 years, diagnosed with T2DM for a minimum of two years, and with HbA1c ≥ 6.5 will be included upon physician referral [18-20].

Exclusion criteria: Individuals with any respiratory issues, serious illness consequences (cardiovascular, renal, visual, cerebral, or peripheral diabetic neuropathy), neurological disorders, musculoskeletal disorders, and those who are alcoholics or smokers with T2DM will be excluded from the study [19,21].

The Institutional Research Ethics Committee (IEC-2681) approved the study, and the trial was registered prospectively with reference number CTRI/2024/07/070544. The study will be conducted in accordance with the revised Declaration of Helsinki, 2013. Written informed consent will be obtained from the subjects before their participation, and all study details will be explained. After the recruitment of participants, demographic details, including weight, height, and Body Mass Index (BMI), will be recorded. Every participant will be allowed to adhere to their prescribed medical treatment regimen during the treatment period. If there are any changes, the participant will not be included in any additional analysis, and an intention-to-treat analysis will be employed for data analysis.

Study Procedure

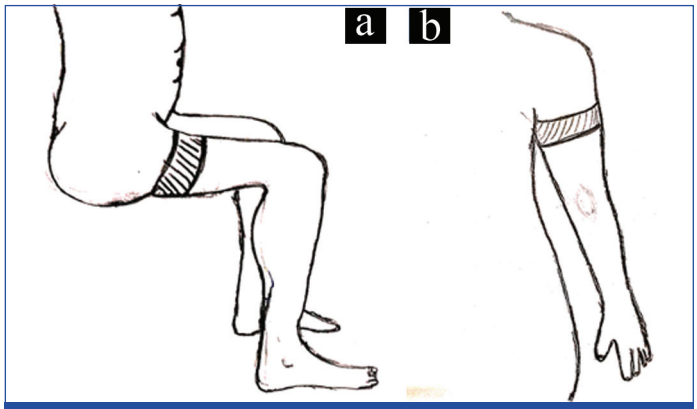
Both groups consist three phases: Warm-up, treatment intervention, and cool-down, conducted three times a week for four consecutive weeks.

Warm-up phase: The six exercises will be performed for five minutes each, requiring one set of 10 repetitions for each exercise. Examples of warm-up exercises include neck tilt, neck rotation, torso rotation, hip rotation, static march, and chest expansion.

Experimental Group (BFRT Group): The main training protocol will include BFRT for both the lower and upper extremities. To restrict blood flow, pressure cuffs will be inflated on the lower limb at 80% [13,22] and the upper limb at 50% [13] of the individual's arterial BP during training. Pneumatic cuffs will be applied to the upper arm, between the biceps brachii and the deltoid, and to the upper thigh, just below the gluteal fold, during training sessions [Table/Fig-1,2] [23].

Mode of exercise prescription with BFR	
Frequency	3 times a week for 4 weeks
Load	20-30% 1RM
Restriction times	5 minutes per exercise
Type	Large muscle groups (arm and leg/ unilateral)
Sets	4
Repetitions	(75 reps)-30×15×15×15
Rest between sets	30 seconds
Limb Occlusion Pressure (LOP)	80% for the lower limb and 50% for the upper limb of Arterial Occlussion Pressure (AOP)

[Table/Fig-1]: Protocol of BFRT.



[Table/Fig-2]: a) Application of BFR cuff during lower limb exercises; b) Application of BFR cuff during upper limb exercises.

- **Examples of lower extremity exercises:**
  1. Leg curls (prone knee flexion/hamstring curls) [13,22]
  2. Leg extensions (knee extension) [13,22]
  3. Straight leg raise (hip flexion) [21]
- **Examples of upper extremity exercises:**
  1. Arm curls (biceps curl) [23,24]
  2. Arm extensions (overhead triceps extension) [23]

Specific instructions will be provided depending on whether the individual will be performing the exercises while sitting, lying down, or standing. Upper-extremity exercises will be done in a series at 20% of the individual's one-repetition maximum (1RM) [13]. Lower extremity exercises will be performed at 20% of 1RM for the first two weeks and at 30% of 1RM for the final two weeks [13].

- **Frequency of exercises for both extremities will be followed as:**

- Three times a week, consecutively for four weeks [13].
- Four sets of 30×15×15×15 repetitions, with a 30-second break between each set [13].
- All warm-up movements will be repeated during the cool-down period.

Control Group {Resistance Training (RT)}:

The RT will focus on both upper and lower body exercises using resistance bands.

- **Upper body exercises will include:**
  1. Rowing motions [25]
  2. Bench press movements [25]
  3. Arm curls [25]
- **Lower body exercises will include:**
  1. Knee extensions [25]
  2. Knee flexions [25]
  3. Forward walking with a resistance band [25]
- Frequency of exercises for both extremities will be:

- Three times a week, consecutively for four weeks [26].
- The programme will prescribe 75% of an individual's 1RM, with three sets of 10 repetitions for each exercise [27], performed at 30-second intervals [25].

Cool-Down Phase: All six exercises from the warm-up phase will be replicated in this phase.

Outcome measurements

Isokinetic Test Measurements:

The isokinetic dynamometer (Easytech genu3) will be used to test the strength of the quadriceps muscle, and the Easytech_isocine2 software will be used to analyse the results. The peak torque ratio will be measured unilaterally with an extension/flexion velocity of 90/90 and with three repetitions.

HbA1c and Lipid Profile Analysis:

Blood from a venous sample will be drawn into a K2 EDTA vial and a red vial for HbA1c and lipid profile {High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL), Total Cholesterol (TC), and Triglycerides (TGs)} analysis, respectively, and sent to the medical laboratory for testing. All three outcome measures (quadriceps strength assessed by peak torque ratio, HbA1c, and lipid profile analysis) will be evaluated at baseline and after four weeks of intervention.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) will be used to analyse the data (peak torque ratio, HbA1C, HDL, LDL, VLDL, TC, and TGs) obtained at baseline and after four weeks of intervention. Depending on the sample size, normality will be assessed. Given the sample size of 58, the Kolmogorov-Smirnov test will be used. Parametric tests will be applied if the data are normally distributed. A paired t-test will be used for within-group data analysis, and the independent t-test will be utilised for between-group data analysis. Non-parametric tests will be applied if the data are not normally distributed; for within-group analysis, the Wilcoxon Signed Rank Test will be used, and for between-group analysis, the Mann-Whitney test will be applied. Throughout the entire course, data confidentiality will be upheld, with only the researcher having access to the specific folders where the data assessment forms are stored.

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