Supplementary File of Statistical Analysis Plan to:

“Does Multifactorial Inspiratory Muscle Training improve Postural Stability and Quality of Life of patients with Diabetes in Pakistan? – A Randomized Controlled Trial

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADDQOL	Audit of Diabetes Dependent Quality of Life
ANOVA	Analysis of Variance
BBS	Berg Balance Scale
CTSIB	Clinical Test of Sensory Interaction in balance
DM	Diabetes Mellitus
FRT	Fall Risk Test
IMT	Inspiratory Muscle Training
LOS	Limits of Stability
MIP	Maximum Inspiratory Pressure
OEP	OTAGO exercise program
PST	Postural Stability Test
SPO2	Saturation of peripheral oxygen

1. STUDY OBJECTIVES

To determine the effects of multifactorial inspiratory muscle training (IMT) combined with Otago Exercise Program (OEP) on balance and quality of life in patients with diabetes.

2. BACKGROUND/INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to either deficiency of insulin or the inability of the body to utilize it. Hyperglycemia ultimately leads to multiple organ damage in patients with uncontrolled diabetes. The incidence occurs mostly at the age of 55 years, equally affecting both genders. The prevalence of diabetes has increased four times in the last three decades worldwide and global prevalence is increasing alarmingly with about 1 out of every 11 individuals having diabetes mellitus with 90% of patients having type 2 diabetes mellitus. The statistical data depicts a huge burden of disease both in morbidity and mortality globally and an anticipated threat on health care system in future. The complications of diabetes have been reported higher in the South Asia region as compared to western counterparts. In Pakistan, according to National Diabetes Survey of Pakistan (NDSP 2016 - 2017), the pooled prevalence of diabetes was projected to be 26.3% affecting 27.4 million people above 20 years of age. These high numbers are directly and indirectly linked with the economic burden on society and ultimately affect the quality of life of diabetics, families, and community.

Clinically, there are different complications (micro & macro vascular) associated with DM and these are main sources of morbidity and mortality. Neuropathy, nephropathy, and retinopathy are the microvascular complications whereas macrovascular complications include cardiovascular diseases, stroke as well as other vascular diseases. Apart from these complications, there are a few other complications including decreased resistance to infections, dental issues, birth complications in gestational diabetes, poor balance, sarcopenia and increased risk of fall and fractures. The reduced strength and endurance of diaphragm, the vital muscle of respiration lead to compromised respiratory functions.

Peripheral neuropathy, retinopathy and vestibular impairments alter the biomechanical stability and strength of postural control in individuals with DM. The instability generates disparity among muscular and neural structures to execute locomotion abilities, so abnormal gait pattern, weakness in lower limb musculature, impair sensory function, diminished reflexes and high fall risk have been observed.

These musculoskeletal complications compromise the mobility level and impede the performance of functional tasks and Activities of Daily Life (ADLs) in patients with DM. The limited movements and participation restrictions in social activities create inaccessibility and dependence on care givers has been increased. The overall activity level has declined and decreases the quality of life of individuals and ultimately developing social and economic burden on community.

Management of DM always emphases to improve the current health status and prevent further complications due to uncontrolled DM. Multiple management approaches have been reported in the literature to maintain adequate glycemic control and manage diabetes related complications and co morbidities. Treatment strategies also focus on maximizing the quality of life and minimize the risk of treatment related complications including hypoglycemia. Balance and postural impairments are common in DM due to neuropathic changes and there are different training strategies that have been documented in literature to improve postural stability and reduce fall risk. The training approaches include Tai Chi, Wii Fit based training, circuit training, strengthening exercises of lower limbs, gait training and task oriented dynamic training to enhance the overall balance abilities.

The central trunk stability and core strength are integral parts of postural stability and balance but there is limited evidence to address these for balance training in DM. There is lacking evidence in literature on specific training targeting the central trunk and core strength to improve the balance ability, reduces fall risk and improve quality of life in DM patients.

Inspiratory Muscle Training (IMT) is a device-based training and widely used therapeutic technique for improving inspiratory muscle strength and endurance, thoracic mobility, exercise capacity, reducing dyspnea and increasing quality of life. Recently, IMT has been used to improve balance and physical performance among elderly.

How IMT is a useful intervention to improve cardiopulmonary function, postural control and quality of life? The underlying mechanism of IMT principal and clinical implications has three-fold mechanisms:

First: Diaphragm thickness and strength enhances balance in two ways. Firstly, there is activation of diaphragm during upper limb movements indicating that the co-activation of diaphragm assists in the mechanical stabilization of the spine. Secondly, it plays a major role in the generation of intra-abdominal pressure which helps in the stabilization of lumbar spine during movements like shoulder abduction and adduction i.e., balance perturbations. These changes will improve lower limb mobility, quadriceps strength, functional performance, postural control response and exercise tolerance among individuals. It creates an overall impact on enhanced balance strategies, physical performance and postural stability in elderly and other pathological conditions including chronic obstructive pulmonary disease (COPD), cystic fibrosis and stroke.

Second: Increases in diaphragmatic mobility and hypertrophy as well as improved neural control and thickness of respiratory muscles including transversus abdominus and internal obliques leads to increase in exercise capacity, pulmonary function and decreased perceived breathlessness and exertion in the patients. It will increase the strength of respiratory muscles ultimately proving it to be an effective treatment strategy in COPD, chronic heart failure, multiple sclerosis and various respiratory diseases.

Third: IMT exerts certain ergogenic effects through increasing diaphragmatic mobility and strength thereby improving the recovery time in sprinters, limiting cardiac sympathetic hyperactivity in cyclists and enhance rowing performance.

Therefore, it can be hypothesized that IMT is not only effective for improving cardiopulmonary function but is also strongly linked with postural stability. The disease burden of DM is growing rapidly, and multiple complications have been reported including cardiopulmonary and high fall risk which declines the overall quality of life. IMT can be useful technique to improve the physical and functional performance, reduce the severity of complications and enable the individuals to become active members of community. The current study is intended to evaluate the dual effects of IMT on postural stability and pulmonary function of diabetic patients.

2.1. STUDY DESIGN

A single-blind randomized clinical trial with two-group pretest-posttest design was used. The study is registered at ClinicalTrials.gov, NCT#04947163 and adheres to the CONSORT reporting guidelines.

2.2. TREATMENT GROUPS

Inspiratory Muscle Training (IMT):

Patients in the IMT group performed home-based IMT twice daily for 12 consecutive weeks starting with at 50% of Maximal Inspiratory Pressure (MIP) and increasing the load progressively, using a protocol already validated and already published elsewhere whereas patients in sham group performed IMT at 15% of Maximal Inspiratory Pressure without increasing the load, using a protocol already validated and already published elsewhere.

Along with IMT and Sham IMT, patients in both the groups underwent the standardized protocol for diabetes by American College of Sports Medicine (ACSM). ACSM recommends 150 minutes of moderate intensity or 60 minutes of vigorous intensity aerobic exercise per week along with minimum 2 non-consecutive days of resistance training per week at intensities between 50% to 80% of 1-repetition maximum (1-RM). The exercises target all major muscle groups using a scheme of 1 to 4 sets of 8 to 15 repetitions per exercise. As the balance of the patients was compromised, the patients also performed home-based Otago Exercise Program (OEP) specifically targeting muscle strengthening and balance re-training exercises for elderly.

2.3. STUDY POPULATION

Patients' diagnosis of Type II DM were recruited through non-probability convenience sampling technique. Patients of both genders with the age ranging from 50-70 years were included in the study. The berg balance score (BBS) of all the patients ranged from 30-50. Exclusion criteria comprised of those with uncontrolled diabetes, hypertension, or disease exacerbation in last 3 months, mini mental state examination (MMSE) score <24, and on oxygen therapy or peripheral oxygen saturation (SPO_2) < 90% during the six-minute walk test (6MWT).

Patients who reported practicing regular physical activity or any balance training in the last 6 months were also excluded. Patients with musculoskeletal comorbidities (e.g., osteoarthritis, low back pain etc.) That may impair exercise performance and previous or current experience with inspiratory muscle training (IMT), patients diagnosed with cardiorespiratory diseases or those with prescription of drugs that effect balance e.g., beta blockers, anti-anxiety, and anti-depressant drugs were also excluded.

2.4. INTERVENTION

Inspiratory muscle training (IMT):

Home-based IMT was performed twice daily for 12 consecutive weeks starting with at 50% of maximal inspiratory pressure (MIP) and increasing the load progressively, using a protocol already validated and already published elsewhere[35].

Sham – Inspiratory Muscle Training:

Home-based sham IMT was performed once a day for 12 consecutive weeks starting with at 15% of maximal inspiratory pressure without increasing the load, using a protocol already validated and already published elsewhere.

2.5. SAMPLE SIZE

A priori sample size of 62 patients was calculated using the G-power program (version 3.1.9.2) at a statistical power 0.85, error probability of 0.05 and effect size of 0.20. However, four additional patients were recruited in each group to compensate for the dropouts.

2.6. STUDY PROCEDURE

The first week was the orientation week where supervised training sessions and written material containing instructions for the patients was provided. Also, the baseline data was recorded this week, where Maximum Inspiratory Pressure (MIP) was assessed though Powerbreathe device whereas lung volumes and capacities were assessed through handheld spirometer. Afterwards, home-based exercise training for a period of 12 weeks was carried out thrice a week on alternate days. However, patients attended one supervised session weekly. Also, a checklist was provided to ensure adherence to protocol and <70% compliance led to the drop out of patient owing to poor compliance. Assessment of fall risk, static & dynamic balance and quality of life was done at baseline and after 12 weeks of intervention.

3. OUTCOME VARIABLES

Outcome measures were categorized into three main groups comprising of nine variables in total. These included Berg Balance Scale (BBS); Biodex Postural Stability system, including seven variables relevant to the tests for static, reactive, anticipatory balance and sensory integration; and audit of diabetes dependent quality of life (ADDQoL) questionnaire.

Berg Balance scale (BBS):

Static and dynamic balance of the participants was assessed through berg balance scale where the patient had to perform 14 predetermined physical tasks assessing different aspects of balance. These included static, anticipatory, dynamic, and sensory balance. Each task was scored from 0 to 4, where 4 indicates the person can complete the task independently, with a final maximal score of 56.

Postural Stability System:

The Biodex Postural Stability system (Biodex Medical Systems, INC. Shirley, New York, USA) is proved to be a highly reliable (ICC = 0.94) measure of postural stability. The system uses a circular moveable platform that provides 20^{o} surface tilt in all 360^{0} directions and is interfaced with a microprocessor-based actuator. Four protocols including Postural Stability Test (PST), Limits of Stability (LOS), Clinical Test of Sensory Interaction in balance (CTSIB) and Fall Risk Test (FRT) score were used for the purpose of this study following already validated protocols.

Static balance of the participants was assessed through Postural Stability Test that measured different indices including the Overall Stability Index (OSI), Anterior-Posterior Index (API), and Medio-Lateral Index (MLI). Reactive balance was assessed via Overall Stability Index (OSI) computed through the Fall Risk Test. Limits of Stability Test was performed to assess the anticipatory balance through the time taken to complete the test (in seconds) and the overall direction control of patients. Sensory integration was assessed by computing the composite score of Clinical Test of Sensory Interaction and Balance.

Audit of Diabetes Dependent Quality of Life (ADDQoL):

The ADDQoL is a reliable (Cronbach's α 0.86) questionnaire used to assesses both overall quality of life as well as the impact of diabetes on specific aspects of life in 19 different life domains. These domains include leisure activities, working life, local or long-distance journeys, holidays, physical health, family life, friendships and social life, close personal relationships, physical appearance, self-confidence, motivation to achieve things, people's reactions, feelings about the future, financial situation, living conditions, dependence on others, freedom to eat, and freedom to drink. A weighted score for each domain was calculated as a multiplier of impact rating and importance rating (ranging from −9 to +3). Lower scores reflected poorer QoL. Finally, a mean weighted impact score (ADDQoL score) was calculated for the entire scale across all applicable domains.

4. STATISTICAL METHODOLOGY

- The statistical analysis was performed using IBM SPSS software (version 26) with the significance tested at 95% confidence interval, $p < 0.05$.
- For descriptive analysis, mean and standard deviations were computed for continuous variables, and frequency with percentages for categorical variables.
- Normality of the data checked through Shapiro Wilk test showed that all the dependent variables were normally distributed ($p > 0.05$).
- For inferential analysis, study hypothesis was tested through 2x2 mixed model analysis of variance ANOVA (pre-post vs intervention type) using Bonferroni post hoc analysis to test both within and between subject factors with the balance tests as the dependent variable.
- For testing the assumptions of mixed ANOVA, homogeneity of covariance matrices was tested through Box's test of Equality of Covariance and assumed to be met if p value >0.05. Normality was assessed through Shapiro Wilk test ($p > 0.05$), homogeneity of variances through Levene's test (>0.05) and sphericity was checked through Mauchly's test of sphericity, for the variables having within subject (repeated measures) factor to determine if the variances of differences between all pairs of level were equal.
- For the variables that did not meet the assumption of sphericity for within subject factors, Greenhouse-Geisser (if $\varepsilon > 0.75$) or Huynh Feldt corrections (if $\varepsilon < 0.75$) were applied.
- Significant interaction and main effects for within and between subject factors were identified, interpreted, and presented through reporting of statistical significance and effect size where applicable.
- The variables in which interaction effect was observed, further analysis was carried out using the independent sample t test for between group comparison and paired sample t test for within group analysis.
- Effect size was interpreted via partial eta square (η_p^2) where $\eta_p^2 > 0.01$ was considered as small, > 0.06 as medium and >0.14 was considered as large effect size.
- Analysis of Covariance (ANCOVA) was also performed to address potential baseline differences between the groups. The analysis was performed to assess the effects of the

intervention on nine outcome variables and adjust for any minor baseline differences present. A Bonferroni correction was applied to account for multiple comparisons. The standard significance level of 0.05 was divided by the number of comparisons (9), resulting in an adjusted significance level of 0.0055 (p = 0.05/9 = 0.0055). This adjusted threshold was used to determine the statistical significance of the results for each outcome variable.