Metabolic, Inflammatory, Cognitive Risk Stratification, Aerobic and Resistant Exercise and e-Health Intervention for patients with Type 2 Diabetes Mellitus

Specific Aims & Hypothesis

The overall objective of this study is to develop a risk stratification score for the sensitive identification of type 2 diabetes (T2DM) middle-aged and older adults with high risk for metabolic health and cognitive impairment (CI), and subsequently conduct and evaluate an Intensive Aerobic and Resistant Exercise Program. The hypothesis of this study is that T2DM patients with high risk for metabolic health and CI can be detected by cognitive tests, biomarkers and self-care assessment, and the identified patients can be managed effectively at primary care settings through an Intensive Aerobic and Resistant Exercise program. Specifically, we aim to:

1. develop a risk stratification score based on metabolic, inflammatory, and cognitive markers to identify high risk T2DM patients for poor metabolic health (glycemic control) and CI;
2. deliver customized Intensive Aerobic and Resistant Exercise Program (IAREP) to high-risk patients and perform preliminary assessment for these patients in improving glycemic control, cognition, muscle strength, and self-care ability.

Background

T2DM is a leading cause of morbidity and mortality among adults worldwide [1], with approximately 5 million diabetes-related deaths which account for 12.8% of all-cause mortality in 2015 [2]. In Asia, T2DM is on the rise, with anticipated patients to increase from 78 million in 2015 to 140 million by 2040 [2]. Asia is emerging as the “diabetes epicenter” due to rapid economic development, urbanization and nutrition transition [3]. T2DM is a complex disease with environmental and genetic contributions that causes many severe complications in middle-aged and older adults, including higher susceptibility for mild cognitive impairment (MCI) and dementia [4]. Given so, the World Health Organization has identified dementia control as a global health priority. In many healthcare systems around the world, dementia and cognitive impairment (CI) is usually underdiagnosed and assumed to be unrelated to other medical problems in patients [5]. Especially for patients living in the community, not much emphasis is placed on cognitive health. Lifestyle interventions including exercise and diet are effective in alleviating diabetes but there are psychological barriers for T2DM patients to commit to regular exercise and diet controls, e.g., fatigue, fear of hypoglycemia, and the lack of measurable biomarkers to indicate the effectiveness or efficiency of such efforts [6, 7]. In this context, identifying and understanding molecular pathogenesis is instrumental in developing scientifically sound lifestyle intervention.

Metabolic, Inflammatory and Neurological mechanism Skeletal muscles are a major organ in glucose uptake and consumption which is regulated by insulins. In T2DM, these muscle cells develop elevated inflammatory status which decreases muscle sensitivity to insulins. It was found that differentiated cultured monocytes isolated from T2DM subjects with insulin resistance secreted more inflammatory cytokines such as Tumour Necrosis Factor alpha (TNF-α), which can induce insulin resistance and mitochondrial dysfunction in muscle cells [8]. TNF-α has been hypothesised to be one of the main activators for the IKK/NF-κB pathway, and this pathway has been postulated to play a role in insulin resistance through higher rates of IKK-mediated serine phosphorylation of insulin receptor substrate 1 (IRS-1) or insulin receptor (IR) [19]. This results in impairment of insulin-induced tyrosine phosphorylation and subsequent inhibition of downstream insulin signalling suppressed expression of molecules such as GLUT4 glucose transporters in the insulin signalling cascade. However, there are currently no reliable serum biomarkers specifically associated with skeletal muscle inflammation [8]. The biomarkers included in this study are to be determined for their specificity in muscle inflammation. Aside from skeletal muscles, insulin resistance has also been found to be an independent risk factor for MCI and may be linked to sporadic Alzheimer’s disease (AD) in the brain [9]. Acting as a long-term neuroprotectant, insulin reduces Amyloid β protein (Aβ) generation and aggregation [10]. Aβ aggregation in the brain results in neurofibrillary tangles and senile

plaques being formed. Insulin resistance thus results in neuronal loss and contributes to the progression of AD. (Figure 1)

Methods & Approach

Research Design - A two-phase study will be conducted. **Phase 1** aims to develop a risk stratification score for the sensitive identification of T2DM middle-aged and older adults with poor metabolic health or CI. **Phase 2** is a pilot randomised control trial (RCT) which aims to evaluate the Intensive Aerobic and Resistant Exercise Program **(IAREP)** on high-risk T2DM patients with poor metabolic health or cognitive functioning in improving glycemic control, cognition and self-care ability. A follow-up process evaluation will assess acceptability, strengths and limitations of Intensive Aerobic and Resistant Exercise Program.

Setting - National University Polyclinics (NUP) provide one-stop medical facilities and healthcare services for patients and their families. A high proportion of patients with chronic diseases such as diabetes, hypertension, hyperlipidemia, stroke etc., is managed by polyclinics. Among all the chronic diseases attended by Singapore polyclinics, diabetes is the third most prevalent chronic disease [34].

Phase 1 - Developing a Risk Stratification Score (RSS)

Eligibility and Recruitment – Convenience sampling will be recruited by NUS research assistants (RAs) at NUP. Recruitment posters will be displayed at NUP. Eligibility of the subjects will be checked. Participants are recruited according to the inclusion criteria: **1) aged 40 to 85; 2) living in the community; 3) diagnosed with T2DM; 4) literate in English or Mandarin; 5) Activities of Daily Living (ADL)-independent; and 6) obtain at least a score of 5 in Short Physical Performance Battery (SPPB) test.** Patients with the following exclusion criteria will be excluded from the study: 1) severe cognitive (e.g., dementia) or psychiatric disorders (e.g., schizophrenia or severe depression); 2) severe hearing or vision impairments; 3) terminally ill medical conditions (e.g., end stage cancer), severe cardiovascular, respiratory (e.g., respiratory failure), or orthopedic conditions (e.g., freeze shoulder); 4) absolute contraindications to aerobic exercise and resistance training programs (e.g., recent myocardial infarction or electrocardiography changes, complete heart block, acute congestive heart failure, unstable angina, uncontrolled hypertension); 5) pregnant or breastfeeding women; 6) uncomfortable with video-recording of intervention sessions.

Sample Size – The participants will be divided into 40-60 and > 60 age groups for *cross-sectional* analyses. The sample size is calculated using RStudio running R version 3.5.1 [35, 36], based on power of 0.8, effect size of 0.15, at significance level of $p<0.05$, considering the multiple independent variables we are analyzing in the regression models (demographics, diabetes self-care abilities), we need 91 participants for both age groups respectively. In consideration of 10% invalid data that might be excluded due to various reasons post-recruitment, and Phase 1 being the recruitment pool for Phase 2 RCT with possible declines towards participation, we propose to have a recruitment target of 300 participants in total. Based on the data from NUP, Jurong Polyclinic has a total of 14888 T2DM patients aged above 40. A daily number of 40-80 T2DM patients visits Jurong polyclinic. Hence, the target recruitment number of 300 participants is achievable.

Risk Stratification Score - Possible risk factors, such as age, education, cognitive test scores, microvascular disease, cerebrovascular disease, acute metabolic event, diabetic foot, and depression/mood disorder will be obtained from the participants during data collection. Outcome measures consist of metabolic profile and cognitive diagnosis defined by formal neuropsychological assessments. Predictors to derive ***RSS*** include inflammatory, lipid, cognitive markers, self-care ability and social-demographic. Logistic regression model will be applied to generate the RSS to predict poor metabolic health and CI in T2DM patients (high, medium, low risk).

Outcome Measures for RSS

1. **Metabolic profile** (HbA1c)
2. **Vascular Dementia Battery (VDB)**: Formal neuropsychological assessments validated for the local population will be conducted [37]. The neuropsychological assessment covers domains in attention,

processing speed, language, visuo-spatial ability, memory and executive function. It is the gold standard to establish the diagnosis of cognitive impairment. It also establishes specific cognitive domain difficulties that T2DM patients may have that could hinder their learning process, so as to customize the intervention delivery for cognitively impaired patients.

Predictors to derive RSS:

1. **Inflammatory profile** (CRP, TNF, IL-6, adiponectin) and **Exerkines** (PCSK9)
2. **Self-care of Diabetes Inventory (SCODI)**: SCODI was developed based on the Self-care of Chronic Illness theory [41]. There are 40 items (5 points Likert type) and 4 dimensions: self-care maintenance, self-care monitoring, self-care management and self-care confidence
3. **Self-rated abilities for Health Practices Scale (SRAHP):** Developed by Becker and Stuifbergen, SRAHP is a 28-item, 5-point scale to measure self-perceived ability to implement health-promoting behaviors. It contains four subscales: Exercise, Nutrition, Responsible Health Practice, and Psychological Well Being. Each subscale has seven items. Rating of each item is from 0 (not at all) to 4 (completely). Total scores range from 0-112. Higher scores indicate greater self-efficacy for health practices.
4. **Social-demographic Data** includes age, gender, ethnicity, religion, marital status, employment status, education level, household type/ownership, living arrangement and number of children. Clinical data includes chronic conditions, blood pressure, height, weight, smoking and drinking status, exercise frequency, and **Short physical performance battery (SPPB)**.

Phase 2 – RCT

Eligibility and Recruitment – Following identification of high-risk patients for poor metabolic health or cognitive functioning, a customized intervention is required to help T2DM patients to better cope with these issues. T2DM patients with poor metabolic health or CI have been reported to demonstrate poor self-care management and medication adherence [25]. High-risk T2DM patients for poor metabolic health or CI will be identified from Phase 1 screening and formal neuropsychological assessments [42], and invited to participate in Phase 2 intervention. A 2-arm/group RCT is adopted.

Group 1: IAREP Intervention A 12-week **Intensive Aerobic and Resistant Exercise Program (IAREP)** aims to train muscle strength, stability and muscle mass and provide health education on lifestyle for the middle-age and older adults with T2DM. Participants with high risk of cognitive impairment will be identified from Phase 1 screening (with the recommended cut-off score). **IAREP** will be conducted for middle-aged and older adults with T2DM. After 12-week of **IAREP**, the same panel of cognitive tests, psychosocial assessments and blood tests will be repeated for participants.

Group 2: Control Participants will receive usual care at NUP, and they will be evaluated with the same panel of cognitive tests, psychosocial survey and blood tests at the end of the study.

Sample Size –For the pilot evaluation sample will choose for 80 subjects in total as Brown (1995) cites a general flat rule to 'use at least 30 subjects or greater to estimate a parameter. Thus, 40 subjects for each independent variable for multiple regression and logistic regression in the pilot evaluation study. A purposive sample of 25-36 participants will be invited for process evaluation.

Randomisation – The participants will be randomly assigned to either e-health intervention or IAREP or wait-list control group with computer-generated random numbers. The intervention groups will engage in **IAREP.** Participants in the control will receive usual care at NUP. The researchers will engage the participants in the **IAREP** and follow up with them during the 12-week intervention period via face-to-face platform or telephone call to ensure compliance.

Outcome Measures – include **Metabolic profile** (HbA1c, plasma insulin), **Vascular Dementia Battery (VDB)**, **Self-care of Diabetes Inventory, Self-rated abilities for Health Practices Scale, SPPB, Rapid Sarcopenia screening (SARC-F), and International Physical Activity Questionnaire – Short Form (IPAQ-SF)** at baseline and post-intervention. People with T2DM experience more progressive skeletal muscle loss than individuals in the non-diabetic population. The SARC-F questionnaire has been developed as a possible rapid diagnostic test for sarcopenia which defined as an age-associated loss of muscle mass. There are 5 SARC-F components: Strength, Assistance with walking, Rise from a chair,

Climb stairs and Falls. The scores range from 0 to 10, with 0 to 2 points for each component. A score equal to or greater than 4 is predictive of sarcopenia and poor outcomes. The IPAQ-SF questionnaire assesses daily physical activities by asking individuals about their engagement in vigorous activities (e.g., heavy lifting), moderate activities (e.g., carrying light loads), and walking over the past 7 days. Participants report how many days they performed these activities and the duration for each. It also includes questions about time spent sitting during weekdays. The IPAQ-SF provides valuable insights into physical activity levels, aiding in health risk assessments and lifestyle improvements.

Process Evaluation – The purpose of process evaluation is to assess the acceptability, strengths and limitations of the **IAREP** based on the participants' perspectives. A qualitative approach with in-depth, focus group discussion (FGD) will be used. Participants from the intervention group will be invited. A semi-structured interview guide will facilitate the questions asked in the FGD. The qualitative data will provide valuable information on the experience and perspectives of the participants.

Data Collection Procedure – Recruitment and data collection will start upon ethical approval. The data collection process, from recruitment to administration of questionnaires, cognitive tests, blood sampling will be done by the research team. Potential participants attending NUP will be screened by primary care nurses, in which participants will be recruited by NUS RAs. All enquiries pertaining to the study will be answered and the study shall commence after obtaining the consent. Confidentiality will be maintained. Self-reported questionnaires will be administered. To avoid study participant selection bias, for the older participants who have difficulty to read and understand the survey, the researchers will use conversational style to engage the participants. The data collection for each participant will take about 40-45 minutes. For process evaluation, the FGD will be conducted according to the participants' preferred language in either English or Chinese. The research assistant will arrange appointments with participants for the FGD. Each FGD consists of 5-6 participants and lasts for 45-60 minutes. Four to five FGDs will be conducted.

Data Analysis – Descriptive statistics will be used to summarize the demographic and clinical data. Analyses will be conducted at a significance level of $p<0.05$ using IBM SPSS (Version 27). In Phase 1, multiple linear regressions will be conducted to examine associations among different measurements. Cognitive impairment based on formal neuropsychological assessments and serum biomarkers such as HbA1c levels will be considered as outcome variables, adjusted by subject demographics, physical measurements, brief cognitive tests (MoCA, SDMT), and self-care ability. Next, logistic regression will be adopted to derive the ***RSS***. Subjects' cognitive status (CI vs non-CI) determined by formal neuropsychological assessment will be its dichotomized outcomes. All risk factors of interest (e.g. sociodemographic, medical history, biomarkers, MoCA and SDMT scores) will be examined using Chi-squared tests or independent t-test to assess association with cognitive status. Significant factors will then be included in the logistic regression model and risk scores will be derived from the respective β-coefficients. The area under receiver operating characteristic (ROC) curve will be assessed to determine the optimal cutoff for the **Risk Stratification Score** (high, medium, low risk).

In Phase 2, outcome measures before and after intervention will be tested for mean differences by paired-sample Student's t-test. For the process evaluation, the audio-recorded FGDs will be transcribed into either English or Chinese verbatim scripts respectively. The transcripts will be analysed in its original language to capture the perspectives of the participants closely. Thematic analysis using Braun and Clarke's [47] six steps of analysis will be applied to provide in-depth and rich analysis of the verbatim. All themes and sub-themes will be translated to English during report writing by the bilingual research team members to ensure the meaning of the translated themes and sub-themes are congruent to the participants' views.

Ethical Issues – Domain Specific Review Board approval will be obtained. The principal investigator and co-investigators will explain the purpose of the research to potential participants. Informed consent will be obtained from the participants prior to data collection. The participants will be reassured that participation in the study is voluntary, and withdrawal from the study will not result in any negative consequences to their usual care.

Research Team

Dr. Wu Xi Vivien is experienced with geriatric and community care, diabetes management and technology-enhanced interventions. Dr. Wu has experience in managing grants. As PI, Dr. Wu oversees

the project, e.g., ethical application, recruitment, intervention, data collection and analysis, report writing, and coordinating with various team members and stakeholders. Dr. Wu, A/P Lu and Dr. Dong have worked on a prior project (CeHP) and published a number of papers on high impact peer-reviewed journals.

A/Prof. Lu Jinhua is an immunologist who contributes to the understanding of inflammatory status in T2DM patients. Adiponectin is a molecule closely related to C1q which is a key molecular target of research in his laboratory. For this project, all laboratory-based work will be conducted in his laboratory.

Dr. Dong Yanhong Catherine has clinical research expertise in neuro-cognition, especially in cognitive screening instrument development and validation for the Singaporean population. She has also developed a brain health program for older adults attending memory clinics and community-dwelling stroke patients. Her role in this project is to train RA for cognitive assessments and analyze the cognitive data.

A/Prof. Zhou Wentao is the Program Director for Master in Nursing, Advanced Practice Nurse (APN) at NUS. Her role is to assist with translating the research findings into practice by developing workshops for APNs and primary care nurses to adopt the **Risk Stratification Score** screening and **IAREP**.

Dr. Yeo Hui Nan is an Associate Consultant, family physician at NUP, and specializes in treatment for T2DM patients. Dr Yeo advises on the feasibility of the study and supports the recruitment process.

Ms. Wang Na is an APN at NUP. She is experienced in primary care for T2DM patients. She supports the recruitment process, logistic issues and the intervention. Dr. Yeo and APN Wang will ensure the continuity of the project by translating the **RSS** and **IAREP** into clinical practice at NUP.

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Please list the references in the order cited in this proposal, including the titles.

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