Ho-DiRECT-Nepal: a food-based educational and home-economics intervention for type 2 diabetes remission

Project Protocol

Background

In Nepal, NCDs, such as diabetes, are steadily increasing. While the lack of a national diabetes registry system and population-wide survey on diabetes makes it difficult to provide an exact estimate of diabetes prevalence in Nepal, recent systematic review reports diabetes prevalence in Nepal at 8.5% [1]. In addition to diabetes, a large number of Nepali people also live with pre-diabetes (prevalence reported at 9.2% [1]), making them increasingly susceptible to diabetes type 2. With increasing diabetes prevalence, complications resulting from inadequately controlled diabetes are also on the rise. Diabetes related complications such as diabetic retinopathy [3] and peripheral neuropathy [4] are increasingly common. Studies mostly conducted in smaller samples and in hospital settings report the prevalence of such conditions to be as high as 45% [5- 6].

Change in food practices and sedentary lifestyle in the urban population has contributed to the increasing NCD prevalence. Of the different known NCD related risk factors, prevalence of low fruit and vegetable consumption, overweight and obesity, raised blood pressure and raised total cholesterol have been reported 'markedly high in the Nepalese population' [10]. Obesity and overweight, measured at BMI ≥ 25kg/m^2, was reported as 21%. [11] The survey was conducted amongst 4200 Nepali adults aged 15-69 years. The percentage for BMI ≥ 23kg/m^2, the preferred BMI mark for overweight and obesity for an Asian population, such as the Nepalese, can be expected to be much higher. The survey revealed that a majority of the Nepali adults (99% of those surveyed) consumed less than five servings of fruits and vegetables combined on an average day [11].

Recent research from the UK offers a radical new diabetes strategy, offering the perspective of shifting primary diabetes management out of medical services into community-ownership: The DiRECT trial [12], funded by Diabetes UK provides valid evidence that diabetes is driven by 'ectopic' body fat accumulation in vital organs- especially liver and pancreas - and that the disease process can be halted by substantial intentional weight loss. A weight-loss of >10 kg. produced remissions of 73% at 1 year, 64% at 2 years amongst people within 6 years of diagnosis and not yet requiring insulin. Remission was achieved by about half of all participants overall[19]. DiRECT used a 3-phase commercial program: (1) 'Total Diet Replacement' using a commercial nutritionally-complete low-calorie formula-diet for about 12 weeks; (2) Stepped Food Reintroduction, introducing the meals for long-term for (3) Structured Weight-Loss Maintenance. This approach is now being adopted within routine UK health services.

This project aims to generate pilot data which in future will aid to translate the randomised-controlled trial [13] evidence that T2D can be prevented, or reversed into remission not requiring medication, for most people, by weight-loss >10kg, into a sustainable community-service in Nepal. This study will strengthen collaborative engagement between UK and Nepal teams for

training, and to refine the food, nutrition and home-economics education basis for a low-cost, locally-sourced, culturally-appropriate intervention.

Research Objectives

General:

- To establish feasibility, and refine protocol and methods, for a novel low-cost, community-owned, programme for weight loss, prevention or remission of type 2 diabetes (T2D), and reduction of cardiometabolic risk factors.

Specific:

- Recruit and train local community health workers, with input from both local doctors and dietitians, and from UK staff experienced in the DiRECT trial and its dietary interventions.
- Establish a training format and resources for all staff involved, to ensure consistency of diet and nutrition messages, robust data collection and scientific methods.
- Establish the accessibility, affordability and acceptability of the Nepalese diet interventions for (i) inducing and (ii) maintaining weight loss.
- Evaluate the potential barriers to diet change among people with diabetes, and their families, and ways to overcome them.
- Evaluate the potential incentives which might optimise uptake and adherence to the programme (eg health improvement, health preservation, economic, domestic, family and community interactions)
- Obtain pilot data from a limited evaluation in a convenient location in people already diagnosed and treated for T2D.

Methodology

Study Design: The project will employ a single-arm intervention and follow-up design for pilot evaluation in ~50 existing hospital patients at Metro Hospital Diabetes Clinic (and other clinics if necessary for recruitment) with T2D of under 2 years duration.

As in the DiRECT and DIADEM-1 trials, glucose-lowering medications will be withdrawn at the start (with a reintroduction protocol according to blood glucose). They will be asked to consume three nutritionally-complete meals of ~280kcal, total ~850kcal/day, to achieve >10kg (ideally >15kg) weight loss over 8-10 weeks, and then local dietary weight maintenance advice. Body weight and HbA1c will be measured at baseline, 12 weeks, 24 weeks and 52 weeks, together with blood pressure, microalbuminuria, liver-function tests and ultrasound liver fat if available.

Participant recruitment

Ambulatory patients (satisfying the inclusion criteria) visiting the hospital(s) will be invited to participate in the program using word-of-mouth and project advertisements placed in each hospital. The participants will be informed verbally about the project details, its objectives,

benefits and risks (we will not rely on written material as literacy is relatively low). Anticipating a 30% drop-out rate, it is planned to recruit at least 80 participants, in order to be able to evaluate the procedures and experiences of n=50 at 6 months.

Inclusion criteria

Patients with type 2 diabetes and prediabetes:

Aged: 30-70 years

BMI ≥ 23 kg/m^2

Diagnosis duration: ≤ 5 years

Exclusion criteria

Weight Loss of >5 kg within last 6 months

Pregnancy/ Lactation

MI or stroke in past 3 months

Chronic pancreatitis, alcohol dependence, psychiatric illness and learning disability

Patients using insulin more than 30 units basal, or other complex insulin regimen (modern medications for T2D are now available or affordable for most patients on Nepal. Only metformin is rovided free, so low dose basal insulin is commonly used for those who can afford it).

Intervention

Participants will be educated about T2D and its multimorbid complications, and offered the dietary intervention program. The health workers and nutritionists will contact the participants on a 2- weekly basis, up-to week – 10 and then 4-weekly. Anthropometric measurements and biochemistry will be conducted routinely (see below- quantitative data). Weight-control support will continue irrespective of T2D remission, aiming to limit related multimorbid conditions. Those not achieving remissions will be referred back to medical services. Patient recruitment and dietary intervention will be conducted within care of diabetes specialists and nutritionists/ dieticians.

The dietary program consists of a food-based alternative to the 'Total Diet Replacement' (TDR) Phase which will last for the first 8 weeks- participants will be requested to follow the 820Kcal TDR diet (Annex-A) that has been prepared by the team using low-cost traditional foods, similar to the Scottish 'No Doubts Diet' based on porridge and lentil soups (see: www.diabetes remission clinical trial.org.uk).

The diet for the maintenance phase, already designed by dietitians from Nepal and UK, will be refined by the nutritionists in the team during the first month.

Study Outcomes

Primary outcome

Remission at 6 months: HbA1c (<48mmol/mol at 12 months), and not receiving glucose-lowering medications for >2 months

Secondary outcomes

)1. Body weight measured with scales at 3, 6 and 12 months

2. HbA1c measured by standard laboratory method at 6 and 12 months

3. Blood pressure measured by electronic sphyhmomanometer at 6 and 12 months

4. Microalbuminuria measured by dipstick and standard laboratory method at 6 and 12 months

5. Liver-function tests measured by standard laboratory method at 6 and 12 months

6. Ultrasound liver fat measured at 6 and 12 months (if available)

7. Quality of Life assessment measured using WHO-BREF – QoL (Nepali version) at 6 and 12 months

8. Glucose-lowering and antihypertensive medications prescribed at 3, 6 and 12 months

9. Participant experience measured by qualitative interviews in a subset at different study stages.

Qualitative Data:

Participants' experience with the dietary program, barriers and facilitators to implementing the program in everyday life, their satisfaction and acceptability of the program will be conducted through qualitative assessments- using interviews.

QoL assessment will be conducted using WHO-BREF – QoL (Nepali version)

Table 1: Outcome evaluation time-frames

	Baseline	TDR		Weight Maintenance Phase		
Weeks	0	4	8	12	24	52
Weight, waist circumference	X	X	X	X	X	X
Height	X					
HbA1c	X			X	X	X
Microalbuminuria/creatinine	X			X	X	X
Blood glucose (fasting &PP)	X	X	X	X	X	X
Blood Pressure	X	X	X	X	X	X
Liver fat (US Abdomen)	X			X		X
Qualitative Assessments- acceptability/satisfaction,	X		X		X	X

barriers/ facilitators, WHO-QOL- BREF (Nepali-Version)						
Medication/Changes	X		X		X	X

Statistics and power

Assuming (conservatively, using DIADEM-1 data) that 12 % would achieve remission without intervention, n=47 would provide power = 90% at $p<0.05$ to detect a remission rate of 30%. Dropouts are assumed to not achieve remission. These observational data would be persuasive for mounting a formal randomised trial.

Statistical Analysis Plan

The primary analysis will estimate the percentage who achieve the primary outcome (HbA1c<48mmol/mol at 12 months) with 95% confidence interval (CI). Losses to follow-up will be treated as not achieving the primary outcome.

Secondary analyses will use logistic regression (?) to assess factors associated with the primary outcome at 3 and 12 months: weight, HbA1c, blood pressure, microalbuminuria, liver- function tests and ultrasound liver fat.

Team (and recruitment if necessary)

Prof Mike Lean

Dr Biraj Karmacharya

Dr Sujata Sapkota

Ms Rashmi Maharjan

Dr Charoula Nikolaou

Dr Abha Shrestha

Ms Ruby Shrestha

Dr Jyoti Bhattarai

Dr Binaya Bhattarai

Ms Bhisma ….

Project Coordinator

Project Management and Governance

Day-to-day management, team coordination and overall supervision by ???? , liaising closely with Prof Lean

Management Group: Research team, medical staff at KUMS-DH, diabetes physicians and health volunteers (trained for the project) … meeting monthly …

Budget Control: KUSMS- DH ……

Ethics approval

Opinions on the need for Ethical approval will be sought from the Nepal Health Research Council (NHRC) and, Kathmandu University Institutional Review Committee (IRC)

Other approvals

Approvals for conducting the study will be sought from all hospitals- Metro Hospital, HAMS & Dhulikhel Hospital