A service evaluation of weight management for glycaemic control and remission of type 2 diabetes using traditional food in Nepal (Ho-DIRECT NEPAL): a single-arm trial

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Summary

Background Remission of early type 2 diabetes (T2D) is possible; however, diet programmes proven effective are unaffordable in many southeast Asian populations where T2D is more frequent and more aggressive at lower body weight and younger age. We evaluate an entirely food-based service.

Methods This study employed a single-arm intervention and follow-up design for intervention evaluation in existing hospital people with T2D of under 5 years known duration. Individuals attending a diabetes clinic in Kathmandu with early T2D (<5 years) aged 30–70 years, BMI ≥23 kg/m^2, were offered a low-cost nutritionally complete diet-programme, using traditional Nepali foods to provide 8-weeks ~850 kcal/day weight loss induction, and then weight maintenance. The participants received 4-weekly dietetic appointments (30–45 min) and verbo-pictorial leaflets using household measures. Glucose-lowering medications (49/70 at baseline) were stopped at baseline or soon after. The study was registered as ISRCTN10671396, testing a traditional food-based intervention for weight loss and T2D remission.

Findings For 70 individuals (45 female) invited between March 19, 2022 and September 19, 2023, baseline mean (SD) age was 48.6 (9.9) years, bodyweight 74.6 (9.5) kg, BMI 29.7 (3.6) kg/m^2, known diabetes duration 2.5 (1.9) years, HbA1c on treatment 8.1 (1.6) %. At 12, 24 and 52 weeks respectively, evaluating n = 44, 46, 45, bodyweight was 70.1 (8.5), 69.8 (8.9), 70.0 (8.8) kg, HbA1c 6.8 (0.9), 6.9 (1.5), 7.1 (1.3) %; HbA1c <6.5% was recorded for 46%, 48% and 36% and remission of T2D (HbA1c <6.5% off medication >3 months) in 43%, 39% and 29%. The main reported adherence barriers were fears of weakness, hunger, and inconvenience during travel. Incentives were ease of the diet, reduced doses and costs of medications, and improved appearance.

Interpretation Traditional food-based weight management can valuably improve control, reduce medication needs, and generate remissions of established T2D, but adherence barriers must be overcome to optimise outcomes.

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Keywords: Type 2 diabetes; Weight management; Ethnicity; Remission; Traditional diet; Nepal

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Research in context

Evidence before this study

Many studies and meta-analyses have established that excess body fat accumulation is the main driver of type 2 diabetes (T2D) in susceptible individuals, and that glycaemia and other markers of T2D improve with weight loss. It is also well established that T2D develops at younger ages, with lower BMI, and follows a more aggressive clinical course, in people of Asian ancestry.

The present study was informed by an umbrella review of systematic trials and meta-analyses of dietary interventions for weight loss and for remission of T2D, conducted by Churuangsuk and colleagues and published in *Diabetologia* in 2020, and by the literature search conducted to inform the STANDby trial of a structured diet intervention for remission of T2D in south Asian people, as recently reported in *The Lancet Regional Health—Southeast Asia* (Sattar et al., 2023). This was itself based on the evidence reviewed for the Diabetes Remission Clinical Trial (DiRECT, published by Lean and colleagues, *The Lancet* and *The Lancet Diabetes and Endocrinology*). These two trials in the UK, plus the DIADEM-1 trial from Qatar (Taheri et al. *The Lancet Diabetes and Endocrinology*), provided the only randomised controlled trial evidence for remission of T2D as the primary outcome from a dietary intervention. All showed quite dramatic 12-month remission rates of 40–60% in recently diagnosed T2D. Such effects are vanishingly unlikely to occur by chance, and some subsequent studies (notably by Hocking et al., 2024) have not employed a control arm (on ethical grounds, to avoid denying a proven treatment). Nepalese clinicians approached the Glasgow DiRECT trial team and provided current data on the prevalence of T2D (8.5% of the population, 25% above age 40 years), on the extremely limited provision of medical care, and on the costs of diabetes care in Nepal, which result in most people with T2D either not attending the medical services or receiving only metformin.

Added value of this study

The current study has provided the first evidence that a simple intervention, advising and demonstrating the use of no-added-cost traditional foods in a nutritionally complete diet plan, can generate a substantial improvement in glycaemic control, with lower need for medication. It resulted in a valuable improvement in diabetes control and remission rate, which could not arise by chance, from relatively modest weight losses. The results are not ideal, with average weight loss about 3 kg maintained at 12 months, and adherence barriers need to be overcome, but the results are encouraging as clinical improvements were greater than for similar weight loss in European populations.

Implications of all the available evidence

Disseminating the new evidence will help to focus the thinking of both people living with T2D, and clinical care providers, in southeast Asia on the power of a non-pharmacological, highly affordable and accessible diet intervention. The intervention is particularly relevant as a treatment for the large numbers of people in low-income and middle-income countries (LMICs) such as Nepal, who cannot access or afford modern western-style diabetes care, and with appropriate health education may form a model for effective self-help or community-based approaches. This paper will contribute importantly to changing the thinking and practice around T2D. The concept of remission of T2D is still new, and unfamiliar to many people especially in LMICs such as Nepal. Making remission, and the potential to delay or avoid complications of T2D, a possibility for these populations is a major implication of the present study. Importantly, future research must now address the educational, practical and cultural barriers to diet change and weight loss in southeast Asia. While using the traditional Nepalese diet as its model in Nepal, the present study has wider implications for diabetes care. Other traditional diets in other countries were associated with historically low rates of overweight/obesity and of the cardiometabolic diseases mediated by adult weight gain, so there is potential to develop nutritionally complete (for essential micronutrients) diets which might help to combat T2D in other settings worldwide.

Introduction

In Nepal, non-communicable diseases (NCDs), such as diabetes, are steadily increasing. While the lack of a national diabetes registry system and limited population-wide survey data makes it difficult to provide an exact estimate, a recent systematic review reports diabetes prevalence in Nepal at 8.5%.[1] In addition to diabetes, many Nepali people also live with pre-diabetes (prevalence reported at 9.2%),[1] thus increasingly susceptible to type 2 diabetes (T2D). With increasing diabetes prevalence, complications resulting from inadequately controlled diabetes are also rising. Diabetes related complications such as retinopathy[2] and peripheral neuropathy[3] are increasingly common. Studies conducted in smaller sample sizes and in hospital settings report the prevalence of such conditions to be as high as 45% of patients.[4,5]

Change in food practices and sedentary lifestyle in the urban population have contributed to the increasing NCD prevalence. A 2019 survey of 4200 Nepali adults (aged 15–69 years) found that among the NCD related risk factors, prevalence of low fruit and vegetable

consumption, overweight and obesity, raised blood pressure and raised total cholesterol were all 'markedly high in the Nepalese population'.[6] Almost all those surveyed consumed less than five servings of fruits and vegetables combined on an average day.[7] Obesity and overweight, measured at BMI ≥25 kg/m^2, was reported as 21%.[6] The proportion with BMI ≥23 kg/m^2, the preferred safe upper BMI for Asian populations, can be expected to be much higher.

Historically considered permanent and inevitably progressive, and overtaking type 1 diabetes as a cause of vascular complications, disabilities and premature mortality, T2D has recently been proved, in well-conducted randomised controlled trials (RCTs), to be reversible into remission (HbA1c below 6.5% without medication for ≥3 months) by dietary intervention.[8] Mean weight losses of 8–12 kg, within 2–6 years of diagnosis, generated remission rates of 40–60% overall at 12 months, and for over 70% at both 1 and 2 years for those who lost >10 kg.[9–11] The key to effectiveness appears to be loss of ectopic fat in liver and pancreas, high in both European and Asian people with T2D.[12–14] While this evidence is rapidly changing the priorities for diabetes care in Western countries, for most people in low-income and middle-income countries (LMICs) and across South Asia, including Nepal, the formula diet interventions used in the RCTs are unaffordable. However, a mean weight loss of only 7–8 kg was necessary to remove ectopic fat and achieve 40% remissions in South Asians with early T2D, who had a considerably lower baseline weights.[13] This is well within the range achievable with inexpensive food-based dietary interventions. This research has also offered the possibility of a radical new diabetes strategy, potentially shifting some primary diabetes management out of medical services into personal or community-ownership.

The present translational project aimed to establish, as a proof of concept, whether T2D can be reversed into remission not requiring medication, by modest weight-loss, which might potentially be achievable for many through a sustainable community service in Nepal and reduce demands on stretched medical services. The study has consolidated collaborative engagement between UK and Nepal research and clinical management teams for training and to refine the food, nutrition and home-economics education basis for a low-cost, locally sourced, culturally appropriate intervention.

The general research objective was to establish intervention feasibility, and refine methods, for a novel low-cost weight loss programme for prevention or remission of T2D, and reduction of cardiometabolic risk factors. Specific steps included diet and meal design and pilot testing, and then training local health workers, with input from both local doctors and dietitians, and from UK staff experienced in the DiRECT trial and its dietary interventions. This training ensured consistency of diet and nutrition messages, robust data collection and scientific methods to evaluate accessibility, affordability and acceptability of the Nepalese diet interventions for (i) inducing and (ii) maintaining weight loss. Qualitative research, led by a local specialist qualitative researcher, sought to identify potential barriers to diet change among people with diabetes, and their families, and ways to overcome them, and potential incentives which might optimise uptake and adherence to the programme.

Methods

Study design

This study employed a single-arm intervention and follow-up design for intervention evaluation in existing people with T2D of under 5 years known duration. The study was registered as ISRCTN10671396, testing a traditional food-based intervention for weight loss and type 2 diabetes remission. Participants were asked to consume three nutritionally complete meals of ~280 kcal, a total ~850 kcal/day, to achieve >10 kg weight loss over 8 weeks, and then dietary weight maintenance advice. As in the DiRECT and DIADEM-1 trials,[9–11] most glucose-lowering medications were withdrawn at the start (with a reintroduction protocol according to blood glucose), some up to 8 weeks later, at clinicians' discretion. Body weight and HbA1c were measured at baseline, 12 weeks, 24 weeks, and 52 weeks, together with blood pressure, lipid profile, and renal function tests at baseline and 12 weeks. Liver fat content was estimated semi-quantitatively, using the Siemens ACUSON NX3 Elite Ultrasound System. All the scans were conducted by the same radiologist and classified during the scanning using ultrasound B-mode. The descriptors used were: Mild (Grade I): diffusely increased hepatic echogenicity but periportal and diaphragmatic echogenicity is still appreciable; Moderate (Grade II): diffusely increased hepatic echogenicity obscuring periportal but diaphragmatic echogenicity is still appreciable; and Severe (Grade II) diffusely increased hepatic echogenicity obscuring periportal as well as diaphragmatic echogenicity is still appreciable.

Study participants

People with T2D visiting the hospital clinics were invited to participate and informed about the project's details, objectives, possible benefits, and risks. Written consent was obtained before enrolment. The people with T2D diagnosed within 5 years; aged 30–70 years; BMI ≥23 kg/m^2 were included in the study. People with weight loss of >5 kg within last 6 months; pregnancy or lactation; myocardial infarction or stroke in previous 3 months; chronic pancreatitis; alcohol dependence; psychiatric illness; learning disability; using insulin >30 units basal-only (an available treatment for T2D in Nepal hospital clinics).

Ethics and approvals statement

Ethical approvals for this service evaluation were obtained from Nepal Health Research Council (21/2022 P) and the

Institutional Review Committee of Kathmandu University School of Medical Sciences (KUIRC-19/22), and approvals were provided by the management of Dhulikhel Hospital, and Metro Hospital (Kathmandu) for conducting the study.

Intervention

Participants were given brief reminders about T2D and its multimorbid complications, and the dietary intervention program was offered as potentially providing benefits. A research assistant contacted participants to offer support and encouragement by telephone every 2-weeks to week 12, then 4-weekly to 12 months and asked them to visit the clinic for study assessments at weeks 8, 12, 24 and 52. Weight-control support continued irrespective of T2D remission, aiming to limit related multimorbid conditions.

The program commenced with a Weight Loss Induction Phase of 8 weeks, using a diet plan of ~850 kcal/day with 58% Energy (%E) from carbohydrate, 19 %E protein, and 23 %E fat. This was followed by a Weight Loss Maintenance diet plan starting at 1200 kcal/day with 49–56 %E from carbohydrate, 17–23 %E protein, and 27–28 %E fat. These two diet plans were designed and pre-piloted using local low-cost traditional foods to provide recommended dietary allowances for all essential micronutrients, based on experience with the Scottish 'No Doubts Diet' (based on porridge and lentil soups plus fruit and bread),[15] and pre-tested amongst Nepalese volunteers for acceptability. Details of the diet intervention are shown in Supplemental Information.[16]

Study outcomes

The primary outcome was HbA1c with T2D remission defined as <48 mmol/mol, with no glucose-lowering medication for >3 months). For the present study, HbA1c <48 mmol/mol, with no glucose-lowering medication at the 12-week assessment was also considered indicative of remission, most participants having stopped glucose-lowering medication at baseline or soon after. Secondary outcomes were body weight, blood pressure, serum creatinine, plasma lipids. These data all used routine, quality-controlled, and clinic measurement methods.

Qualitative data, collected by interviews during weight loss induction and maintenance periods, to evaluate routine practice, were standardised for the present study to explore participants' experiences with the dietary programme, barriers and facilitators to implementing the programme in everyday life, their satisfaction and programme acceptability. These data will be reported in detail elsewhere.

Statistical analysis

Descriptive summary statistics are presented without imputations for missing data. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were calculated for continuous variables. Changes from baseline are reported for body weight, HbA1c, blood pressure, serum lipids, and renal function tests using paired *t*-test methods. One-way ANOVA forrepeated measures was used to compare the mean weight and mean HbA1c over time at 12 weeks, 24 weeks, and 52 weeks. The statistical analysis was performed using STATA 14 (StataCorp, Inc).

Role of the funding source

This study was funded by a grant from the All Saints Educational Trust, an educational charity registered in England. The funder had no role in the study design, conduct, or interpretation of results.

Results

A total of 85 people attending diabetes clinics at Metro Hospital between March 29, 2022 and September 19, 2023, who satisfied inclusion criteria, were invited to participate in this service evaluation, and 70 participants agreed. Socio-demographic characteristics of the study participants are shown in Table 1. At baseline, 21/70

Characteristics	Frequency	%
Age (mean, SD) years	48.6 (9.9)	
Sex		
Female	45	64.3
Male	25	35.7
Marital status		
Married	68	97.2
Single	1	1.4
Widowed	1	1.4
Occupation		
Housewife	29	41.4
Business	19	27.2
Service	15	21.4
Agriculture	1	1.4
Retired	3	4.3
Other	3	4.3
Education		
No formal education	9	12.9
Primary	18	25.7
Secondary	31	44.3
Higher	12	17.1
Duration of diabetes diagnosis (mean, SD), years	2.5 (1.9)	
Weight (mean, SD), kg	74.6 (9.5)	
HbA1c (mean, SD), %	8.1 (1.6)	
BMI (mean SD), kg/m^2	29.7 (3.6)	
Other medical conditions		
High blood pressure	15	21.4
High blood cholesterol	10	14.3
Anxiety or depression or antidepressant medications	2	2.9

Table 1: **Socio-demographic characteristics of the study participants (n = 70).**

were on diet treatment alone for diabetes, and 49/70 were taking glucose-lowering medications (metformin alone n = 29, DPP4i alone n = 6, and combinations of glucose-lowering drugs n = 14, sulphonylurea n = 3, insulin n = 1). Additionally, 21% (15/70) of the participants had a history of hypertension, and 14% (10/70) had high blood cholesterol. Among those, 6/70 were on medication to reduce blood pressure, and 8/70 were on medication to reduce blood cholesterol.

Table 2 shows the effects of the dietary intervention at 12 weeks, when follow-up blood sampling was conducted, on bodyweight, HbA1c, blood pressures, serum lipids (total cholesterol, HDL, LDL, fasting triglycerides), and renal function tests, as changes between baseline and 12-week values. There were statistically significant differences between before and after intervention for bodyweight (P < 0.001), HbA1c (P < 0.001), LDL (P = 0.0009), and creatinine (P = 0.0015). However, there was no statistically significant difference between before and after the intervention for blood pressures, serum lipids (total cholesterol, HDL, fasting triglycerides).

Mild or moderate fatty liver was detected at baseline in 29/70 and 2/70 participants respectively. Paired liver fat data were available for 29 participants, and showed a reduction in liver fat category for 5/29 participants, no change in 23/29 and an increase in liver fat in 1/29 participant.

Table 3 shows the changes in weight, medications, and HbA1c from baseline. Mean body weight at 12, 24, and 52 weeks, with data available from 44, 46, and 45 participants, respectively, was 70.1, 69.8, and 70.0 kg, representing mean (SD) weight losses from baseline of 4.1 (2.5), 4.1 (3.0) and 2.7 (3.1) kg. The mean baseline weight and HbA1c of those remaining at 24 and 52 weeks were very similar to that of the group recruited.

At 12, 24, and 52 weeks respectively, 34/44 (77%), 33/46 (72%), and 26/45 (58%) participants were not taking glucose-lowering medications, and a further 5/44 (11%), 6/46 (13%) and 1/45 (2%), were taking lower doses than at baseline. Mean bodyweight decreased sharply from baseline to 12 weeks, by just over 4 kg. Bodyweights remained relatively constant between 12 and 24 weeks, with a slight increase observed at 52 weeks (Fig. 1). After adjusting for age and sex, a statistically significant difference in mean weight over time was found [P = 0.004].

Fig. 2 shows how study participants' mean HbA1c changed between baseline (when most were taking glucose-lowering medications), and assessments at 12 weeks, 24 weeks, and 52 weeks. The mean HbA1c decreased sharply from baseline to 12 weeks, over the time when pre-study glucose medications were withdrawn for most participants. It remained relatively stable between 12 and 24 weeks, with a slight increase observed at 52 weeks. After adjusting for age and sex, a statistically significant difference in mean HbA1c over time was found [P = 0.001]. The number with HbA1c below 6.5% (<48 mmol/mol), irrespective of treatment, was 20/44 (46%) at 12 weeks, 22/46 (48%) at 24 weeks, and 16/45 (36%) at 52 weeks. Among these, remission of T2D (HbA1c <6.5%, with no glucose-lowering medication at the 12-week assessment and for >3 months at later time-points) was achieved at 12 weeks by 19/44 (43%), at 24 weeks by 18/46 (39%), and at 52 weeks by 13/45 (29%). The number of participants taking medication to reduce blood pressure was 6/70 at baseline, 1/44 at 12 weeks, 1/46 at 24 weeks, and 1/37 at 52 weeks. The number of participants taking medication to reduce serum cholesterol was 8/70 at baseline, 5/44 at 12 weeks, 2/46 at 24 weeks, and 1/37 at 52 weeks. No serious adverse events were reported.

The qualitative research in summary, indicated that declining the invitation to participate, missing data and loss to follow-up were all mainly through difficulties in receiving calls, or in planning follow-up visits because of distance, and work or domestic arrangements. Difficulty adhering to the diet plan was for some through a sense

	Baseline mean (SD)	12 weeks mean (SD)	Mean difference (SD)	P-value
Weight kg (n = 44)	74.2 (8.9)	70.1 (8.4)	4.1 (2.4)	<0.001
HbA1c % (n = 44)	8.2 (1.5)	6.8 (0.9)	1.4 (1.6)	<0.001
Systolic blood pressure (n = 35) mmHg	125 (16)	119 (10)	6 (19)	0.062
Diastolic blood pressure (n = 35) mmHg	77 (8)	75 (7)	2 (12)	0.183
Total cholesterol (n = 31) mg/dl	178 (46)	156 (36)	22 (60)	0.050
Triglycerides (n = 33) mg/dl	199 (103)	195 (86)	4 (97)	0.809
HDL (n = 29) mg/dl	47 (9.9)	49 (7.6)	2 (11.8)	0.387
LDL (n = 26) mg/dl	92 (30)	69 (34)	24 (32)	<0.001
HDL/LDL Ratio (n = 26)	2.19 (1.00)	1.44 (0.73)	−0.58 (0.72)	<0.001
Urea (n = 32) mg/dl	22 (9)	23 (8)	1 (13)	0.622
Creatinine (n = 33) mg/dl	0.78 (0.2)	0.65 (0.1)	0.13 (0.2)	0.002
Sodium (n = 30) mEq/L	139 (1.9)	138 (1.8)	0.7 (2.6)	0.159
Potassium (n = 30) mEq/L	4.3 (0.3)	4.2 (0.3)	0.1 (0.3)	0.359

Table 2: **Changes between baseline and 12 weeks (n = 44), assessed by paired-sample *t*-test.**

Baseline	Week 12 (n = 44)	Week 24 (n = 46)	Week 52 (n = 45)
Body weight change (kg: mean (SD))	−4.1 (2.5) P < 0.001	−4.1 (3.0) P < 0.001	−2.7 (3.1) P < 0.001
Number (%) off glucose-lowering medications	34 (77%) P < 0.001	33 (72%) P < 0.001	26 (58%) P = 0.004
Number (%) with HbA1c below 6.5% (below 48 mmol/mol)	20 (46%) P < 0.001	22 (48%) P < 0.001	16 (36%) P < 0.001
Number in remission (%)	19 (43%) P < 0.001	18 (39%) P < 0.001	13 (29%) P < 0.001

Paired *t*-tests were used for body weight. Fisher exact tests were used for the others. P-values are from comparisons with baseline (please note that P-values are not adjusted for multiple comparisons, but this will not affect the overall conclusions of the paper).

Table 3: **Changes from baseline in body weight, medications and HbA1c, including remissions of diabetes, defined as HbA1c <48 mmol/mol, without glucose-lowering medication at the 12-week assessment, and for >3 months at later points.**

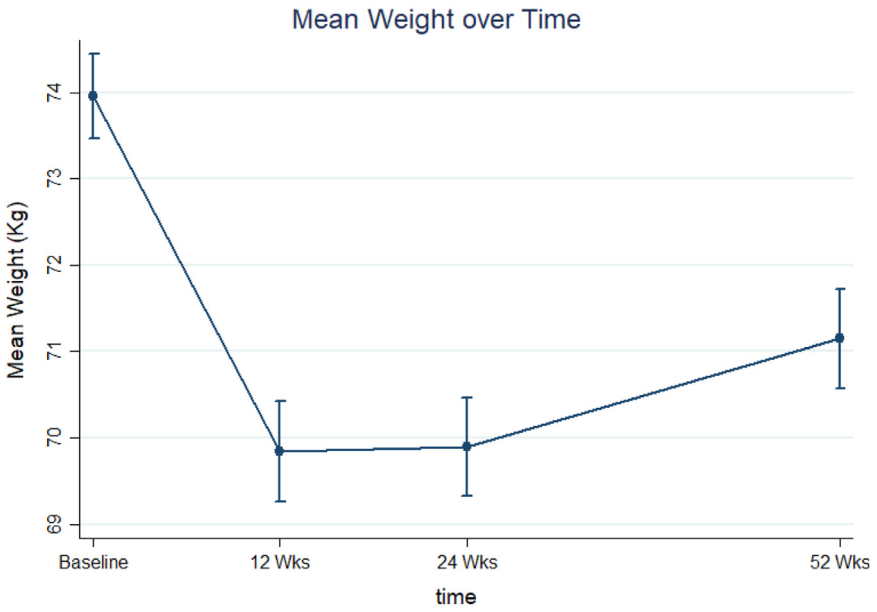

Fig. 1: Body weight at baseline and study assessments at 12, 24 and 52 weeks, of participants with weight data at every time-point. Data is shown in mean (SE) format.

or fear of weakness with low-calorie diet, and others found the diet too monotonous (they wanted a variety of foods). Some participants reported a belief that medications are more powerful than diet, and that the diet alone is insufficient for the disease. Detailed qualitative research findings will be published elsewhere.

Discussion

The present results have demonstrated consistent metabolic improvements from the diet intervention, and a remission rate amongst those with data of 39% at 24 weeks, 29% at 52 weeks, in very typical people with T2D attending diabetes clinics in Nepal. Improvements were

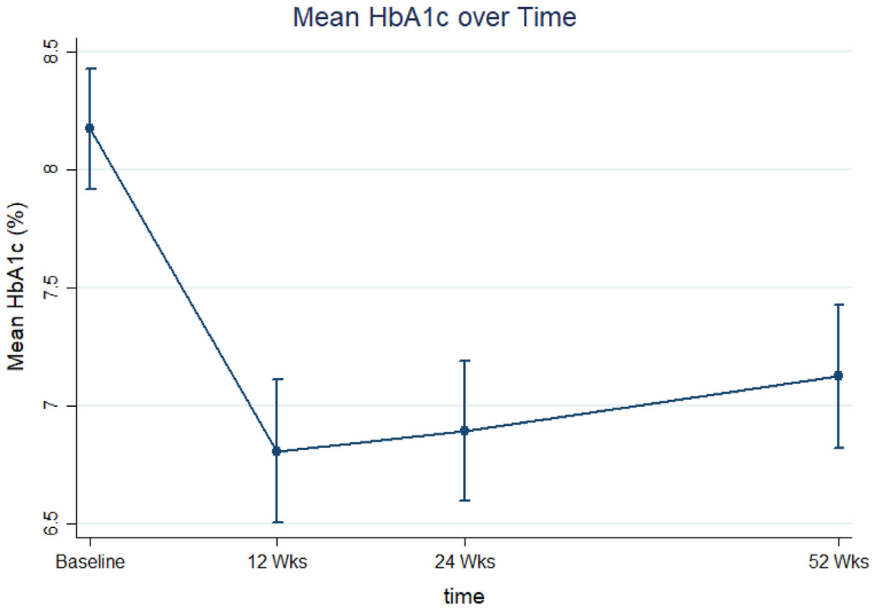

Fig. 2: HbA1c at baseline (when most were taking glucose-lowering medications), and at 12 weeks, 24 weeks, and 52 weeks, of participants with HbA1c data at every timepoint. Most medications were withdrawn at baseline or before 8 weeks. Data is shown in mean (SE) format.

observed for most clinical indicators for metabolic NCDs, including HbA1c, LDL-cholesterol, and creatinine, with fewer participants requiring medications for diabetes, hypertension and dyslipidaemia. While the single-arm study design cannot itself prove causality, our results are unlikely to have occurred by chance. They are consistent with results from randomised controlled trials of effective weight management but were achieved using a simple diet plan for weight management which incurred no new cost to participants. In keeping with DiRECT and all the subsequent highly effective weight management interventions for remission of type 2 diabetes, the diet for weight loss induction was provided as a simple fixed plan, while dietary advice for longer term weight loss maintenance was tailored to individuals and guided by weight changes. The study was conducted in Kathmandu, so the diet intervention was designed for people with T2D from urban areas, although some did travel in from rural areas. The study adopted one of the most familiar traditional Nepalese food patterns, which was accessible easily for all participants. An important principle of the diet interventions used for remission of T2D is to follow a fixed repetitive diet plan for the weight loss induction phase, rather than a menu approach which tends to encourage greater energy consumption. Recognising that T2D is a very serious disabling and life-shortening disease, but reversible in its early stages, the need for substantial weight loss is very great and diet needs to be considered as a serious treatment for several weeks. In the event, adherence was good enough to achieve remissions for almost 30%, but still clearly suboptimal. The qualitative research, to be analysed and published elsewhere, will help to improve the content and presentation of diet approaches in Nepal. We did not address physical activity in the present study. While increasing physical activity improves mood, and reduces cardiometabolic risk markers, people in real world settings who are overweight and particularly those with T2D who have a paucity of type 1 oxidative muscle fibres, find it very difficult to make sustained increases in physical activity. No increase was achieved in DiRECT despite encouragement at every visit and provision of step-counters to try to increase daily steps[17] and there is no published evidence that remission of diabetes can be achieved through physical activity. Likewise, the diabetes prevention studies and other weight management interventions have found rather little effect from physical activity, compared to a dominant effect from diet.[18]

The diet programme generated only modest mean weight losses, indicating relatively limited diet programme adherence, likely reflecting the current incorrect general perceptions among Nepalese people, revealed in the qualitative research, that diet is less effective than medication for controlling T2D, coupled with a fear that weight loss might cause weakness. Some of our secondary outcome results are hard to explain. For example, the observed decline in serum creatinine is somewhat surprising, as baseline levels were not elevated, and the intervention is unlikely to have caused a major change in muscle mass. The mean weight change was not very great, but we believe a fall in serum triglyceride might still have been expected. It is possible that some participants stopped taking lipid-lowering medication as well as glucose-lowering medication as was reported in a Danish study of people who achieved remission of T2D.[19] The results do however provide proof of concept that intentional weight loss, for overweight Nepalese people with T2D, is likely to improve diabetes control and to generate remissions, as it has in other populations. While the weight loss achieved was less than that with low energy formula diets, clearly suboptimal and needing to be improved, it was encouraging to see relatively large improvements in HbA1c and a greater remission rate than might be expected from similar weight loss in people of European ancestry.[9,13] There was substantial loss to follow-up between the baseline and the next visit, mainly because of difficulties over work and transport for participants who lived far away. Thereafter, having lost those more remote participants, we saw remarkably good participant retention. The overall loss to follow-up (about 35% over 12 months) was actually not very different from that found in many dietary weight management interventions in higher income western countries. DiRECT was unusual in also being able to collect data from non-research routine NHS primary care attendances, not available in Nepal where there is no UK-style primary care.

T2D is a very large and increasing health and social burden in many LMICs, particularly among South Asian populations such as Nepal, where healthcare resources and services are extremely limited and still dominated by demands to address the high prevalence of infectious diseases. While medical care of T2D has improved dramatically in high-income countries, that has been principally through the development of ever more expensive medications and services to manage the vascular complications and associated chronic diseases such as hypertension. Very often, the main underlying driver of T2D, adult weight gain in susceptible individuals who accumulate organ-damaging ectopic fat, has been relatively ignored, allowing the disease process to continue, ultimately leading to organ failures.[20] Life expectancy is still reduced by several years with T2D, despite modern management, to a degree comparable with some primary cancers.[21] While the new GLP-1 agonist drugs may improve weight management, their optimal effects for T2D still rely on dietetic support for behavioural change, and they are unlikely to become affordable to many in countries like Nepal.

The DiRECT trial,[9,10,12] funded by the patient-led charity Diabetes UK, provided strong evidence that diabetes is driven by 'ectopic' body fat accumulation in vital organs, especially the liver, and pancreas, and that

the disease process can be halted for most people when this fat is reduced to normal levels, by substantial weight-loss. Diet thus proved considerably more effective than any medication for T2D control. With weight loss >10 kg, remissions were 73% at 1 year and 64% at 2 years amongst people within 6 years of diagnosis and not yet requiring insulin. With a mean weight loss of 10 kg, remission was achieved by 46% overall at one year. DiRECT used a structured program, Counterweight-Plus, involving (1) 'Total Diet Replacement' using a commercial nutritionallycomplete low-calorie formula diet for about 12 weeks; (2) Stepped Food Reintroduction, introducing the meals for long-term for (3) Structured Weight-Loss Maintenance. The 'DiRECT Principles[22] were published to outline the key components for an effective remission programme. Formula meal replacements were optionally used for one meal daily during weight loss maintenance. The population studied in DiRECT were all European and had a very high BMI. The subsequent DIADEM-1, STANDby and DiRECT-AUS trials used almost identical interventions to achieve similarly high remission rates of over 40% at 12 months in Arab, South Asian and Australian people with T2D,[11,13,23] and longer follow-up results point towards avoidance of clinical complications of T2D in those who achieve remissions.[24,25] Remission rates in the control groups (who were all volunteer individuals interested in improving glycemia and remission) were under 12%, mostly under 5%, at 12 months. These striking and highly consistent results have already led to national remission programs adopting the 'DiRECT Principles',[19] but this intervention model is unaffordable for low and middle-income countries. The present study provides data that might herald a new view of diabetes and a new low-cost model to improve its practical management in LMICs. Perceptions about T2D and the effectiveness of dietary weight management still need to be addressed, with the aim of improving adherence to diet programs.

This study has strengths in using a robust, clinically relevant, primary outcome measure and being based in a routine care real-life setting, in a very typical clinical population in Nepal. That setting inevitably entailed limitation through adherence to the support and follow-up plan, with a loss to follow-up of 25/70 (35.7%) over 12 months. However, this is a typical or even good follow-up rate for clinical research in an LMIC, from which well-conducted clinical research is scarce. The loss to follow-up may have introduced bias, as participants lost to follow-up may have been less successful with the intervention. Conversely, their health may have improved, allowing them to move elsewhere for employment. There is no comparable existing research evidence on diet composition and adherence for T2D in Nepal. While better results might be expected in those who remained in the study, those with data at 12, 24 and 52 weeks had clinical characteristics including HbA1c, at baseline, broadly similar to those of the whole sample (Table 3), which suggests that loss to follow-up or missing data did not introduce serious bias. The drop-outs were slightly younger and included proportionally more men, perhaps suggesting occupational migration. The single arm study design would be considered a serious limitation for many trial purposes but was chosen under the reasonable assumption that a remission rate of greater than 20% could not occur by chance within the routine care of established clinic patients, with mean baseline HbA1c (on treatment) of 8.1%. This figure is higher than in control arms of published T2D remission studies, making the present study relatively conservative. The single arm design was preferred because committing volunteers to a control arm and denying a treatment which is proven, albeit in different settings, with a visible, desired result, is ethically questionable. It is also practically problematic since participants allocated to a control arm are likely to drop out or to corrupt the conventional analysis by obtaining the desired treatment (for weight loss) elsewhere.

The results showed that most of the weight loss, and the rapid fall in HbA1c despite stopping glucose-lowering drugs, occurred in the first 12 weeks. The internationally agreed criteria for remission of diabetes cannot be applied at 12 weeks, but proportion who had HbA1c below 48 mmol/mol, without glucose-lowering medication was similar at 12 and 24 weeks. As with other dietary studies, there is a ubiquitous problem in achieving long term maintenance of weight loss and T2D remission. People with T2D all have excess body fat, in abnormal 'ectopic' sites, regardless of BMI.[14] Most do not regard their diets, which allow them to reach and maintain a weight which is higher than optimal, as 'abnormal', and many do not consider themselves sufficiently overweight to cause a serious disease, or recognise the seriousness of T2D until permanent disabling complications have arisen. Intentional weight loss and maintenance always require some degree of dietary limitation, of quantity and composition, and thus incurs costs to quality of life by interfering with normal social interactions and behaviours. The principle behind the diet plan used for the present intervention was to capture the simplest elements of a traditional Nepalese diet whilst ensuring that sufficient essential micronutrients were included for a period of weight loss. Having demonstrated that it can be used to achieve worthwhile metabolic improvements and remissions, public and community initiative can now translate the principles for wider adoption. To improve adherence, further research is needed to improve diet composition and education. Health promotion can also valuably focus on the seriousness of T2D for younger people, and its reversibility with quite modest weight loss. A wider public campaigning can valuably highlight the association of weight gain and T2D to (i) urban migration, (ii) reduced physical activity and (iii) provision of foods and

drinks manufactured in western style. Most importantly, the public campaigning can encourage a celebration of traditional, local foods amongst young people.

Contributors

The study was conceived and designed by ML, JB, SS, CN and BK. The intervention detail was defined and conducted by JB, CN, SS, and BB. Funding acquisition was facilitated by ARL. Data collection was done by BB and RK. Data analysis was done and verified by PR, AS, and AMcl. Primary manuscript writing was by ML and PR. All authors contributed to manuscript review and editing. All authors had full access to all the data and agreed to submit for publication.

Data sharing statement

De-identified participant data will be made available for appropriate scientific purposes on request to the communicating author, after publication of the planned analyses. The study protocol is published at ISRCTN.

Declaration of interests

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100465.

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