Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial

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ABSTRACT
Objective To determine the extent to which intensive dietary intervention can influence glycaemic control and risk factors for cardiovascular disease in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment.

Design Randomised controlled trial.

Setting Dunedin, New Zealand.

Participants 93 participants aged less than 70 years with type 2 diabetes and a glycated haemoglobin (HbA1c) of more than 7% despite optimised drug treatments plus at least two of overweight or obesity, hypertension, and dyslipidaemia.

Intervention Intensive individualised dietary advice (according to the nutritional recommendations of the European Association for the Study of Diabetes) for six months; both the intervention and control participants continued with their usual medical surveillance.

Main outcome measures HbA1c was the primary outcome. Secondary outcomes included measures of adiposity, blood pressure, and lipid profile.

Results After adjustment for age, sex, and baseline measurements, the difference in HbA1c between the intervention and control groups at six months (−0.4%, 95% confidence interval −0.7% to −0.1%) was highly statistically significant (P=0.007), as were the decreases in weight (−1.3 kg, −2.4 to −0.1 kg; P=0.032), body mass index (−0.5, −0.9 to −0.1; P=0.026), and waist circumference (−1.6 cm, −2.7 to −0.5 cm; P=0.005). A decrease in saturated fat (−1.9% total energy, −3.3% to −0.6%; P=0.006) and an increase in protein (1.6% total energy, 0.04% to 3.1%; P=0.045) in the intervention group were the most striking differences in nutritional intake between the two groups.

Conclusions Intensive dietary advice has the potential to appreciably improve glycaemic control and anthropometric measures in patients with type 2 diabetes and unsatisfactory HbA1c despite optimised hypoglycaemic drug treatment.

Trial registration Clinical trials NCT00124553.
Moreover, the addition of insulin for patients on maximally tolerated sulphonylureas and metformin has the potential for additional weight gain and increased risk of hypoglycaemic episodes.14

The major studies that showed the benefits of diet treatment were carried out before the recommendations that led to the greatly increased prescription of hypoglycaemic and cardioprotective drugs and were of short duration.15–19 The Lifestyle Over and Above Drugs in Diabetes (LOADD) study therefore investigated the extent to which intensive evidence based dietary advice is able to influence glycaemic control and risk factors for cardiovascular disease in people with type 2 diabetes who had persistent hyperglycaemia and remained at high cardiovascular risk despite their drug treatment having been optimised according to current guidelines.

METHODS

The LOADD study, a randomised controlled trial of six months’ duration, took place at the Department of Human Nutrition, University of Otago, Dunedin, New Zealand, between October 2006 and July 2009.

Participants

We recruited potential participants through local general practices, hospital diabetes clinics, the regional diabetes retinal screening service, pharmacies, and the local diabetes society and through advertising in the local weekly newspaper. We required them to be under 70 years of age, be resident within the Dunedin city boundary, have been diagnosed with type 2 diabetes more than 3 months before study entry and, despite having been given standard dietary advice by dietitian, doctor, or nurse and prescribed oral hypoglycaemic agents, insulin, or both, have persistent unsatisfactory glycaemic control defined as HbA1c more than 7%. As the study was aimed at people at high risk of cardiovascular disease, we also required participants to have at least two of the following three characteristics: overweight or obesity (body mass index ≥25), hypertension (currently prescribed antihypertensive drugs or blood pressure >140/90 mm Hg despite optimised antihypertensive drug treatment), and dyslipidaemia (currently prescribed lipid modifying drugs or one or more of total cholesterol >5.2 mmol/l, low density lipoprotein cholesterol >3.5 mmol/l, triglycerides >2.0 mmol/l, and high density lipoprotein cholesterol <1.0 mmol/l despite optimised lipid modifying drug treatment). Pregnancy, the presence of a serious chronic illness other than diabetes considered likely to need a start or change of drug treatment during the trial, or unwillingness to attempt to comply with intensive dietary advice if randomised to the intervention group excluded participation.

Potential participants were screened by telephone by a research nurse or research dietitian and then by a medical officer during a clinical assessment that included a blood test for measurements of HbA1c and fasting lipids. We considered participants suitable for randomisation to the intervention or control group if they fulfilled the entry criteria and were receiving appropriate maximally tolerated classes and doses of drug treatments for blood glucose, blood pressure, and lipid control according to national and international guidelines for the management of type 2 diabetes.17–19 Those who fulfilled the entry criteria but were not being treated with appropriate drugs or in whom dosage adjustment was needed were recommended an optimised treatment regimen. We reassessed their eligibility for randomisation after stabilisation on their new treatment regimen, requiring that appropriate drug treatment had been started and adjusted according to guidelines. All clinical assessments and adjustments of treatment were carried out under the supervision of one of the authors (JM), who has more than 30 years of experience as a consultant physician with expertise in diabetes and an involvement in developing guidelines nationally and internationally. All randomised participants were thus considered not to be well controlled despite receiving optimised drug treatments.

Randomisation

Two research assistants not involved with the study did the randomisation in blocks of 10 by using sealed opaque envelopes and with stratification according to sex and HbA1c (7–8%, or >8%) measured at the clinical

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Flow chart of participants.
Baseline characteristics of study participants in intervention and control groups. Values are numbers (percentages) unless stated otherwise.

| Table 1 | Characteristics                          | Intervention (n=45) | Control (n=48) |
|---------|-----------------------------------------|--------------------|---------------|
|         | Mean (SD) age (years)                   | 56.6 (8.8)         | 58.4 (8.8)    |
| Women   |                                        | 28 (62)            | 27 (56)       |
| Self identified ethnicity: |                                      |                    |               |
| New Zealand European |                                  | 34 (76)            | 42 (88)       |
| Māori    |                                        | 1 (2)              | 2 (4)         |
| Pacific Island |                                  | 3 (7)              | 0 (0)         |
| Other    |                                        | 7 (16)             | 4 (8)         |
| Current smoker |                                  | 4 (9)              | 3 (6)         |
| Mean (SD) duration of diabetes (years) |                        | 8.7 (6.4)          | 9.0 (5.8)     |

Drug groups:

- Oral hypoglycaemic agents only: 31 (69) vs 34 (71)
- Insulin only: 1 (2) vs 0 (0)
- Insulin and oral hypoglycaemic agent(s): 13 (29) vs 14 (29)
- Lipid modifying drugs: 26 (58) vs 31 (65)
- Angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or both: 24 (53) vs 30 (63)
- Other antihypertensive agents: 14 (31) vs 23 (48)
- Aspirin: 17 (38) vs 31 (65)

Intervention

Both groups received one-off “push play” advice on physical activity—that is, on the desirability of achieving at least 30 minutes of physical activity of moderate intensity on most, if not all, days of the week. Both groups continued to attend their usual provider of clinical care for diabetes (general practitioner or hospital diabetes clinic). Participants in the control group were given an undertaking that they would receive further advice depending on the outcome of the trial, and they had no further contact with the researchers until they and those randomised to receive intensive dietary intervention were reassessed at the end of the six month trial.

The intensive dietary intervention was based on the evidence based recommendations of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes. The recommended distribution of macronutrients was protein 10-20% of total energy, total fat less than 30% of total energy, saturated fat less than 10% of total energy or less than 8% of total energy if low density lipoprotein cholesterol was raised, polyunsaturated fatty acids less than 10% of total energy, and carbohydrate 45-60% of total energy. The target for dietary fibre intake was 40 g/day—or 20 g/4184 kJ (1000 kcal)—about half of which was intended to be soluble fibre. For participants who were overweight or obese, the recommendation was to achieve modest (at least 5%) weight loss. We translated recommended total energy intake and nutrient distribution for each participant into foods, recipes, and meals on the basis of the initial three day weighed diet record, personal preference, budget, and sociocultural factors. The emphasis was on appropriate food quantities, vegetables, fruit, legumes, wholegrain cereals, fish (preferably oily), nuts, low fat dairy products, and appropriate fats and oils. Meat, when consumed, was to be lean.

Each participant had two individual sessions with the study dietitian within the first month after randomisation, then monthly sessions for five months. One group education session within the first two months and a telephone call between visits, as deemed necessary by the dietitian, provided opportunities to reinforce the dietary advice and give additional support. Participants’ family members were encouraged to attend dietary education sessions. Clinical measurements (anthropometric measures and blood pressure) and blood tests (HbA1c and lipids) at three months were an integral component of the six month intervention and provided a means of offering feedback on progress and further support.

Study outcomes

The primary outcome measure was HbA1c. Secondary outcomes included changes in hypoglycaemic drugs (type and dose), weight, body mass index, waist circumference, blood pressure, fasting plasma glucose, and lipid profile.

Measurements were made at baseline and six months. We recorded demographic data at baseline, a nurse administered a questionnaire on medical history, drugs, and physical activity, and a dietitian gave instruction on completion of a three day weighed diet record (two weekdays and one weekend day) at baseline and six months. Trained research nurses made resting blood pressure (triplicate) and anthropometric (duplicate) measurements under standardised conditions and took blood samples after a 10 hour overnight fast. These measurements were made on two separate occasions (within one week) and averaged. Blood samples were analysed at the Lipid and Diabetes Laboratory of the Department of Human Nutrition, University of Otago, using methods previously described by our laboratory. Southern Community Laboratory Dunedin analysed urine samples. Urinary creatinine was measured on a Roche Hitachi 911 analyser using the Jaffé reaction method. Urinary albumin was assayed on a Roche Modular analyser using the Tinaquant immuno-turbidmetric assay.

Statistical analysis

We based an estimate of the sample size for the study on data from the Otago diabetes register. Calculations used a standard deviation of 1.4% and a correlation between measures of 0.8. We needed to enrol at least 41 people in each treatment group to detect a difference of 0.57% in HbA1c with 80% power at the 5% level of significance allowing for a 10% dropout rate. We analysed the data in accordance with a modified intention to treat principle, using a pre-established analysis plan. We used analysis of covariance, with adjustment for sex, age, and the baseline measure, to
compare the differences between the treatments at six months. We used two sided significance tests throughout. The results are presented as differences (with 95% confidence intervals) between the two groups. We made no adjustment for multiple testing.

RESULTS

Figure 1 shows the flow of participants through the study. Of 104 eligible participants randomised, 94 (90%) completed the six month study. Table 1 provides key characteristics of the two groups. Most participants in both groups described themselves as New Zealanders of European descent. However, the intervention group was ethnically more diverse—one quarter were of Mori, Pacific Island, Lebanese, or Indian ethnicity. Participants in the intervention group were slightly younger, but smoking status, duration of diabetes, and use of hypoglycaemic drugs were similar in the two groups. Improvements occurred in most clinical and laboratory measures in patients with type 2 diabetes at high risk of cardiovascular disease whose control was considered to be unsatisfactory despite optimum drug treatment according to international management guidelines.14-19 This effect occurred despite the fact that some of the patients considered to be on maximum drug treatment were able to reduce their dose of tablets or insulin. The magnitude of the reduction in HbA1c (0.4%) is comparable with that seen in clinical trials when a new drug has been added to conventional agents.24-26 For example, the use of vildagliptin together with insulin results in HbA1c reductions of up to 0.7% compared with the effects of insulin alone.25 The reduction in HbA1c may seem to be modest. However, the relation between HbA1c and intervention group, four of the 14 patients on insulin had their insulin doses decreased by up to 81 units. No serious adverse events were reported.

Table 3 shows the nutritional intakes calculated for the 78 participants for whom complete three day weighed diet records were available at both baseline and six months. A decrease in saturated fat (P=0.006) and an increase in dietary protein (P=0.045) were the most striking differences between the two groups. Analysis of the food groups showed greater consumption of low fat dairy products and nuts in the intervention group. At six months, a higher proportion of total energy consumed by intervention participants compared with control participants was from low fat dairy products. The magnitude of the reduction in HbA1c may seem to be modest. However, the relation between HbA1c and

Table 2 | Primary and secondary end points at baseline and six months and adjusted differences between intervention and control groups. Values are means (SD) unless stated otherwise

| Measures                        | Intervention (n=45) | Control (n=48) | Difference* (95% CI) P value*Baseline 6 months Baseline 6 months |
|---------------------------------|--------------------|---------------|---------------------------------------------------------------|
| HbA1c (%)                       | 8.9 (1.4)          | 8.4 (1.0)     | -0.4 (-0.7 to -0.1)                                           | 0.007 |
| Glucose (mmol/l)                | 9.0 (2.6)          | 8.1 (2.2)     | -0.6 (-1.5 to 0.3)                                           | 0.181 |
| Weight (kg)                     | 98.4 (18.7)        | 96.3 (18.0)   | -1.3 (-2.4 to -0.1)                                          | 0.032 |
| Body mass index†                | 35.1 (6.1)         | 34.3 (5.8)    | -0.5 (-0.9 to -0.1)                                         | 0.026 |
| Waist circumference (cm)        | 114.1 (13.7)       | 108.9 (13.6)  | -1.6 (-2.7 to -0.5)                                         | 0.005 |
| Systolic blood pressure (mm Hg) | 131.9 (15.8)       | 127.8 (15.6)  | -1.4 (-6.1 to 3.2)                                         | 0.536 |
| Diastolic blood pressure (mm Hg)| 79.8 (9.0)         | 76.5 (8.7)    | -0.5 (-3.0 to 2.0)                                         | 0.673 |
| Total cholesterol (mmol/l)      | 4.35 (0.93)        | 4.11 (0.97)   | -0.14 (-0.38 to 0.10)                                      | 0.248 |
| HDL cholesterol (mmol/l)        | 1.04 (0.22)        | 1.04 (0.25)   | 0.01 (-0.04 to 0.05)                                          | 0.747 |
| LDL cholesterol (mmol/l)        | 2.52 (0.83)        | 2.30 (0.82)   | -0.15 (-0.35 to 0.06)                                        | 0.162 |
| Triglycerides (mmol/l)          | 1.71 (0.83)        | 1.67 (1.04)   | 0.01 (-0.26 to 0.28)                                         | 0.933 |
| Uric acid (µmol/l)              | 302.1 (78.9)       | 313.3 (81.5)  | -1.5 to 0.3                                                  | 0.140 |
| Urine albumin:creatinine ratio‡  | 7.5 (24.6)         | 7.1 (23.8)    | 3.4 (-0.5 to 7.4)                                           | 0.089 |

HDL=high density lipoprotein; LDL=low density lipoprotein.
*Adjusted for age, sex, and baseline measurements.
†Calculated as weight in kilograms divided by square of height in metres.
‡Complete urine samples not obtained for two participants in intervention group and one participant in control group; albumin was measured in milligrams per litre, and creatinine was measured in grams per litre; urine albumin:creatinine ratio values were log transformed.
complications of diabetes is continuous, so that any reduction in HbA1c is likely to reduce the risk of complications. In the UKPDS, in which no threshold for risk was seen, each 1% reduction in mean HbA1c was associated with reductions in risk of 21% for any end point.27 As expected from other studies in which patients with type 2 diabetes on various drugs have been followed prospectively, participants in the control group showed no improvement in glycaemic control, despite increased doses or changes in their hypoglycaemic drugs.10 Measures of adiposity improved in parallel with improvements in HbA1c, and the differences between the two groups were also significant. This is in contrast to insulin treatment, of which weight gain is a common side effect.14 Failure to show significant differences in blood pressure or in total cholesterol and low density lipoprotein cholesterol between the groups may be due to the fact that values were close to target levels at the start of the study and that current antihypertensive and lipid modifying drugs are effective.

Comparison with other studies
Nutritional modification has repeatedly been shown to have the potential to improve glycaemic control and reduce cardiovascular risk in both type 1 and type 2 diabetes,11 19 20 28 but no definitive data show its potential in the context of intensive drug treatment as currently recommended. In a small study, Aas and colleagues suggested that intensive lifestyle intervention was as effective as insulin in improving glycaemic control in patients with type 2 diabetes on maximal tolerated doses of oral hypoglycaemic agents, with additional benefit in that lifestyle change was associated with weight loss whereas those randomised to insulin gained weight.28 In another small study, Goudswaard and colleagues confirmed in a similar group of patients that an intensive educational programme, including dietary instruction, had the potential to improve glycaemic control to the extent that delaying the introduction of insulin was considered appropriate.30 Both the ICAN study and Look AHEAD study also showed benefits from a lifestyle intervention among overweight and obese patients with type 2 diabetes, but in those studies the patients did not necessarily have poor glycaemic control and no attempt was made to optimise drug treatment beforehand29 31; weight loss, rather than glycaemic control, was the primary outcome. No studies to date have approached the clinical question considered here, which is increasingly relevant as patients with type 2 diabetes are prescribed an increasing number of drugs and, like populations of non-diabetic people worldwide, are becoming increasingly overweight and obese.32 33 Excess adiposity is associated not only with more difficult to control levels of blood glucose and diabetes related complications but also with an increased risk of other serious morbidities and mortality, including an increased risk of several important cancers.34

Strengths and limitations of study
The high retention rate throughout the study is a major strength, as is the fact that the dietary intervention was based on internationally accepted guidelines, those of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes.1 The non-prescriptive dietary approach, consideration of participants’ background and socioeconomic circumstances, and non-reliance on commercially prepared meal replacements may have contributed to the high retention rate. The fact that participants were volunteers who were prepared to make substantial lifestyle changes, as well as the six month duration of the intervention, may be perceived to be weaknesses of the study. However, a high level of motivation and compliance is an essential prerequisite for all therapeutic options in diabetes, and the efficacy of the dietary intervention was the focus, rather than its maintenance. The need to explore various approaches to self management, including the adoption and maintenance of nutritional changes, is widely recognised.35

Implications
The Diabetes and Nutrition Study Group guidelines are less prescriptive than many earlier sets of dietary advice. They acknowledge that several dietary patterns are less prescriptive than many earlier sets of dietary guidelines emphasise that appropriate nutritional changes, is widely recognised.35

Table 3 | Nutrient intakes at baseline and six months and adjusted differences between intervention and control groups at six months. Values are means (SD) unless stated otherwise

| Nutrients                  | Intervention (n=39)       | Control (n=39) | Difference* (95% CI) | P value* |
|----------------------------|---------------------------|---------------|----------------------|---------|
| Baseline                   | 6 months                  | Baseline      | 6 months             |         |
| Energy (kJ)                | 8020 (1899)               | 7845 (2085)   | -334 (-1082 to 414)  | 0.376   |
| Protein (% TE)             | 19.7 (3.7)                | 19.2 (3.5)    | 0.5 (0.04 to 3.1)    | 0.045   |
| Total fat (% TE)           | 30.9 (6.1)                | 29.8 (6.1)    | -1.1 (-4.6 to 1.0)   | 0.211   |
| Saturated fatty acids (% TE)| 11.2 (3.2)               | 11.3 (3.5)    | 0.1 (-3.3 to 0.6)    | 0.006   |
| Polyunsaturated fatty acids (% TE)| 5.2 (1.6) | 5.1 (2.0) | -0.1 (-0.7 to 3.2)  | 0.211   |
| Carbohydrate (% TE)        | 47.5 (7.1)                | 50.1 (7.5)    | 0.5 (-2.3 to 3.2)    | 0.731   |
| Dietary fibre (g)          | 25.7 (6.3)                | 26.4 (5.6)    | 0.3 (-0.2 to 6.1)    | 0.064   |

*Adjusted for age, sex, and baseline measurements.

TE=total energy.
Individualised intensive dietary advice has the potential to improve glycaemic control and anthropometric measures in patients with type 2 diabetes and unsatisfactory HbA1c, despite optimised hypoglycaemic drug treatment
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Accepted: 19 May 2010