# The Finnish Diabetes Prevention Study

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The aim of the Finnish Diabetes Prevention Study is to assess the efficacy of an intensive diet–exercise programme in preventing or delaying type 2 diabetes in individuals with impaired glucose tolerance (IGT) and to evaluate the effect of the programme on the risk factors of atherosclerotic vascular diseases and the incidence of cardiovascular events. In this ongoing study, a total of 523 overweight subjects with IGT based on two oral glucose tolerance tests were randomized to either an intervention group or a control group. The main measure in the intervention group is individual dietary advice aimed at reducing weight and intake of saturated fat and increasing intake of dietary fibre. The intervention subjects are individually guided to increase their level of physical activity. The control group receives general information about the benefits of weight reduction, physical activity and healthy diet in the prevention of diabetes. A pilot study began in 1993, and recruitment ended in 1998. By the end of April 1999 there were 65 new cases of diabetes, 34 drop-outs and one death. The weight reduction was greater (–4·6 kg) at 1 year in the intervention group ($n = 152$) than in the control group ($n = 143$, –0·9 kg, $P < 0·0001$), and this difference was sustained in the second year of follow-up. At 1 year 43·4 % and at 2 years 41·8 % of the intervention subjects had achieved a weight reduction of at least 5 kg, while the corresponding figures for the control subjects were 14·0 and 12·0 % ($P < 0·001$ between the groups). At 1 year the intervention group showed significantly greater reductions in 2 h glucose, fasting and 2 h insulin, systolic and diastolic blood pressure, and serum triglycerides. Most of the beneficial changes in cardiovascular risk factors were sustained for 2 years. These interim results of the ongoing Finnish Diabetes Prevention Study demonstrate the efficacy and feasibility of the lifestyle intervention programme.

**Type 2 diabetes: impaired glucose tolerance: prevention: diet: exercise: lifestyle**

Type 2 diabetes is an increasingly common disease in most affluent societies, and its incidence is rapidly increasing in many developing countries. In Europe, the prevalence of type 2 diabetes has been estimated to increase from 16 million to 24 million within the next 10–15 years, and worldwide the number of diabetic patients may even double within the same period (Amos *et al*. 1997). The health burden caused by type 2 diabetes is mainly due to atherosclerotic vascular diseases and microvascular and neuropathic complications of diabetes. In particular, coronary heart disease, strokes and peripheral vascular diseases account for most of the excessive morbidity and mortality among type 2 diabetic patients (Kannel & McGee, 1979; Pyörälä *et al*. 1987). In Finland both total mortality and the risk of cardiovascular mortality and morbidity are at least three- to fourfold in middle-aged and elderly diabetic patients as compared with the respective non-diabetic population (Uusitupa *et al*. 1993; Kuusisto *et al*. 1994; Niskanen *et al*. 1998). Also the costs of diabetes are rapidly increasing in the community, mainly due to an increasing need for the treatment of late complications of diabetes, but also due to intensified treatment of cardiovascular risk factors and hyperglycaemia. Therefore it is reasonable that growing interest has focused on the primary prevention of type 2 diabetes through lifestyle changes and possibly using also pharmacological agents (Pan *et al*. 1997; Diabetes Prevention Program Research Group, 1999; Eriksson *et al*. 1999). In addition to preventing type 2 diabetes, early interventions in subjects with a high risk of type 2 diabetes are aimed at preventing atherosclerotic vascular diseases and other late complications of diabetes (Knowler *et al*. 1995; Uusitupa, 1996). If successful in the long term, this approach will

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result in better health status among people at high risk of type 2 diabetes, and may also cut the cost of treatment and health consequences of diabetes.

The main risk factors of type 2 diabetes are obesity, central type obesity, sedentary lifestyle, high-fat diet rich in saturated fatty acids, low intake of dietary fibre and large doses of diuretics and certain beta-blocking agents (Tuomilehto *et al*. 1997). Besides these environmental factors, type 2 diabetes is known to have a strong genetic component (Hamman, 1992). Some studies suggest that disturbances in intra-uterine nutrition can contribute to the development of type 2 diabetes later in life (Hales *et al*. 1991). The principal metabolic defects in type 2 diabetes are impaired insulin action (insulin resistance) and defects in insulin secretion (DeFronzo, 1997; Shepherd & Kahn, 1999). There is a great deal of evidence that weight reduction and increased physical activity can improve the insulin action and correct disturbances in cardiovascular risk factors in patients with type 2 diabetes and in subjects with impaired glucose tolerance (IGT) known to be at increased risk of type 2 diabetes (Knowler *et al*. 1995; Uusitupa, 1996).

In a Swedish non-randomized study (Eriksson & Lindgärde, 1991), a 6-year intervention with diet and exercise advice resulted in a 50 % reduction in the incidence of diabetes in middle-aged men who volunteered to participate in the intervention group compared to those who were not willing to participate and thus served as controls. Pan *et al*. (1997) reported on the marked decline in cumulative incidence of diabetes among subjects with IGT in the city of Da Qing in China after 6 years of intervention with either a diet, exercise or combined diet and exercise programme. The incidence of diabetes was 67·7 % in the control group compared with 43·8 % in the diet group, 41·1 % in the exercise group and 46·0 % in the diet plus exercise group. Interestingly, the intervention was equally successful in normal-weight and obese people. The incidence of new diabetes was exceptionally high in this study where randomization was made by the clinic, not by the individual.

The Finnish Diabetes Prevention Study (DPS) was planned to provide a definite answer to the question whether primary prevention of type 2 diabetes by lifestyle modification is possible (Eriksson *et al*. 1999). This question has also been raised by other research groups (Diabetes Prevention Program Research Group, 1999). Our study differs from other ongoing studies in that we are using a non-pharmacological approach only. Furthermore, the principles of our intervention programme can be easily applied to the primary health-care system, where most subjects at high risk of diabetes will be treated if (and when) the primary prevention of type 2 diabetes becomes common practice.

In this paper, the study design and the interim results based on the 1- and 2-year follow-up examinations are presented, with special emphasis on the feasibility of the lifestyle intervention. A detailed description of the study design and 1-year results for a smaller sample size have recently been published elsewhere (Eriksson *et al*. 1999).

## Study design, subjects and methods

The DPS is a multi-centre study with five participating centres in Finland, located in Helsinki, Kuopio, Oulu, Tampere and Turku. Altogether 523 subjects with IGT have been randomized. The recruitment started in 1993 in connection with a pilot study, and was completed in May 1998. Subjects were recruited from epidemiological surveys and by opportunistic population screenings with special emphasis on the high-risk groups, i.e. obese subjects with a positive family history of type 2 diabetes. All the subjects were randomized to either the diet-and-exercise intervention group or the control group. The randomization was made by centre, sex and mean 2 h glucose concentration (7·8–9·4 mmol/l or 9·5–11·0 mmol/l).

The main examinations at the baseline and follow-up visits are listed below.

- medical history, physical examination
- anthropometric measurements
- height, weight, BMI
- waist and hip circumferences, waist-to-hip ratio
- sagittal and transverse diameter
- lean body mass and fat mass
- serum lipids, PAI-1, fibrinogen
- blood pressure
- liver function
- thyroid stimulating hormone
- uric acid
- oral glucose tolerance test (OGTT), glucose, insulin
- glycated haemoglobin $A_{1c}$
- GAD-antibodies
- electrocardiogram (ECG)
- 2 km walking test
- 24 h exercise diary plus 12 month exercise questionnaire
- 3 d food record
- health status
- RAND 36-item health survey (Hays *et al*. 1993)
- human leucocyte antigens
- other genetic factors

The annual examinations include medical history, physical examination, 2 h OGTT, serum lipids, blood pressure and ECG. Detailed information on the methodology is available elsewhere (Eriksson *et al*. 1999).

### Inclusion and exclusion criteria

Overweight subjects (BMI $> 25\ kg/m^2$) aged 40–64 years with IGT were eligible for the study. The diagnosis of IGT was based on the WHO criteria (WHO, 1985), i.e. subjects with fasting plasma glucose $<7{\cdot}8$ mmol/l and 2 h plasma glucose with 7·8–11·0 mmol/l were classified as having IGT. In 90 % of randomized subjects the diagnosis of IGT was based on the mean of two 2 h OGTTs, in others the diagnosis was based on one OGTT only (Eriksson *et al*. 1999). All subjects gave written informed consent, and the study protocol was approved by the Ethics Committee of the National Public Health Institute in Helsinki. The subjects were excluded if they had a previous diagnosis of diabetes other than gestational diabetes. Other exclusion criteria were vigorous exercise, active glucose-lowering treatment of any kind other than routine dietary and health advice, and chronic disease and medical conditions which could make 6-year survival improbable or interfere with glucose metabolism.

The DPS was designed to be large enough to detect a 35 % reduction in diabetes incidence with an intensive diet and exercise intervention with 80 % power (Eriksson *et al.* 1999).

## Intervention programme

At the start of the study, subjects in the control group received general information about healthy diet and the importance of weight reduction and physical activity in prevention of diabetes. Additional routine advice will be given at the annual follow-up visits. The control subjects were also advised to reduce the use of alcohol and to stop smoking as appropriate.

The intervention group received frequent dietary advice tailored to each person individually, as well as group sessions. The ultimate goal was to reduce BMI to less than 25 kg/m$^2$, but a weight loss of 5–10 kg, depending on the degree of overweight, was the target for many subjects. The baseline 3-day food records were used for planning dietary advice which was given by trained nutritionists. The subjects were advised to consume a diet with more than 50 % of daily calories from carbohydrates; less than 10 % from saturated fat and 20 % from mono- and polyunsaturated fat, or up to 25 % if the surplus is from monounsaturated fat (this option only if the weight goal has been achieved) (Sarkkinen *et al.* 1996). The dietary cholesterol intake was to be less than 300 mg daily, and an increase of fibre intake to 15 g per 1000 kcal or more is encouraged. During the first year of intervention there were seven dietary advice sessions for those in the intervention group, and every 3 months 3-day food records were completed. The information obtained through these records was used in compiling further dietary advice. The study protocol also allows the use of a very low-calorie diet if BMI is over 30 kg/m$^2$ after 6 months.

The subjects in the intervention group are individually guided to increase their physical activity. Both aerobic exercise and resistance training are recommended, and if possible supervised sessions in each centre are organized. Compliance with the exercise programme is regularly monitored by interviews. Furthermore, a 2 km walking test is organized annually for both groups to monitor physical fitness.

The main outcome measures, secondary outcome measures and possible *post hoc* analyses which could be carried out are summarized below.

*Main end point*

- new diabetes confirmed in two subsequent OGTTs

*Other outcome measures*

- glucose tolerance
- insulin values
- cardiovascular risk factors
- cardiovascular risk score
- cardiovascular morbidity and mortality
- quality of life

Post hoc *analyses*

- impact of baseline characteristics on outcome measures
- impact of actually observed lifestyle changes on primary and secondary outcomes
- impact of genetic factors on the development of diabetes, or response to intervention
- in Kuopio:
  - progression of carotid atherosclerosis by ultrasound
  - frequently sampled intravenous glucose tolerance test: insulin secretion, insulin action

The primary outcome measure is the development of diabetes, and all study subjects have an OGTT at each annual visit. If the first OGTT shows diabetic values, the diagnosis is confirmed by another OGTT at least 1 week after the first one.

## Results

All the data given in this paper are preliminary and are based on the different numbers of observations due to the different time of outset of the study in each study centre. The recruitment started in 1993 in Helsinki and Kuopio, and other centres joined the trial later on. Table 1 shows the baseline characteristics for the intervention and control groups based on the current database. The study subjects are middle-aged and obese, with the mean BMI over 31 kg/m$^2$. The mean values of fasting and 2 h serum insulin values were high. The mean fasting plasma glucose level was around 6 mmol/l, and 2 h glucose around 9 mmol/l. Serum total cholesterol was close to that seen in recent Finnish population-based studies, whereas the average HDL-cholesterol was low and triglycerides high. No significant differences were observed in any of the baseline characteristics between the two groups.

Table 2 summarizes the 1-year changes in anthropometric variables, glucose and insulin values, serum lipids and blood pressure. The mean weight loss was 4·6 kg in the intervention group and 0·9 kg in the control group. Most of the weight loss can be attributed to the loss of fat mass, as shown by the changes in anthropometric measures. In both groups, a slight increase was found in fasting plasma glucose values, albeit less in the intervention subjects, while 2 h glucose decreased significantly more in the intervention group. Furthermore, fasting and 2 h insulin values decreased significantly more in intervention subjects than in control

**Table 1.** DPS – preliminary results*

| Variable | Intervention group | Control group |
|---|---|---|
| Age (years) | 53·7 | 52·1 |
| BMI (kg/m$^2$) | 31·6 | 31·2 |
| Waist (cm) | 103·3 | 101·4 |
| Fat mass (kg) | 32·5 | 31·0 |
| Sagittal diameter (cm) | 26·3 | 26·1 |
| fP-glucose (mmol/l) | 5·9 | 6·1 |
| 2h-glucose (mmol/l) | 9·0 | 8·9 |
| fS-insulin (mU/l) | 14 | 15 |
| 2 h insulin (mU/l) | 102 | 95 |
| $HbA_{1c}$ (%) | 5·6 | 5·5 |
| Lipids | | |
| Total C (mmol/l) | 5·64 | 5·66 |
| LDL-C (mmol/l) | 3·64 | 3·62 |
| HDL-C (mmol/l) | 1·22 | 1·23 |
| Triglycerides (mmol/l) | 1·71 | 1·77 |
| Systolic BP (mm Hg) | 141 ($n$=160) | 137 ($n$=150) |
| Diastolic BP (mm Hg) | 86 ($n$=160) | 85 ($n$=150) |

* Baseline characteristics: $n$=159–210 in the intervention group and 148–201 in the control group due to the incomplete database of this ongoing study.

**Table 2.** DPS – preliminary results: 1-year changes

| Variable | Intervention group ($n=152$) | Control group ($n=143$) | $P$ for difference between groups |
|---|---|---|---|
| Weight (kg) | –4·6 | –0·9 | 0·0001 |
| BMI (kg/m$^2$) | –1·7 | –0·3 | 0·0001 |
| Waist circumference (cm) | –3·2 | –0·4 | 0·0001 |
| Hip circumference (cm) | –3·5 | –1·2 | 0·0001 |
| Sagittal diameter (cm) | –2·7 | –1·7 | 0·0220 |
| Fat mass (kg) | –3·5 | –0·6 | 0·0098 |
| fP-glucose (mmol/l) | +0·1 | +0·3 | 0·0055 |
| 2 h glucose (mmol/l) | –0·9 | –0·3 | 0·0049 |
| fS-insulin (mU/l) | –3 | –1 | 0·0192 |
| 2 h insulin (mU/l) | –38 | –10 | 0·0017 |
| $HbA_{1c}$ (%) | –0·1 | +0·1 | 0·0927 |
| Systolic BP (mm Hg) | –6 | –3 | 0·0753 |
| Diastolic BP (mm Hg) | –4 | –1 | 0·0044 |
| Total cholesterol (mmol/l) | –0·11 | –0·13 | 0·7943 |
| HDL cholesterol (mmol/l) | +0·05 | +0·01 | 0·0675 |
| Triglycerides (mmol/l) | –0·21 | –0·03 | 0·0049 |

subjects. Systolic and diastolic blood pressure decreased more in the intervention group than in the control group. The decrease in serum triglycerides was also greater in the intervention group.

At the 2-year examination, the mean weight loss was 4·2 kg in the intervention group and 0·1 kg in the control group ($P < 0·0001$). Consequently, the intervention group showed a persistent reduction in body fatness and an improvement in glucose tolerance. Also blood pressure and serum triglyceride values tended to change in favour of the intervention subjects (data not shown).

At 1 year 43·4 % and at 2 years 41·8 % of the intervention subjects had achieved >5 kg weight loss, while the corresponding figures among the control subjects were 14·0 and 12·0 %, respectively ($P < 0·001$). We also analysed the 2-year data according to the amount of weight loss (>5 kg versus 5 kg or less) in the whole group, i.e. combining the intervention and control subjects. The changes in glucose tolerance, fasting and 2 h postglucose insulin values, systolic and diastolic blood pressure, and serum HDL-cholesterol and triglycerides were significantly greater among subjects with a greater weight loss after 2 years' follow-up than among the rest (data not shown).

In a subgroup analysis of subjects participating in the intervention in Kuopio, beneficial changes in diet and physical performance based on the 2 km walking test were also observed. In the intervention group there was a significantly greater reduction in energy intake after 1 year as compared to the control group (–294 versus –86 kcal, $P = 0·04$). In both groups there was a reduction in the proportion of energy from fat (–3·5 versus –3·7 E%, NS) and from saturated fat (–2·3 versus –1·7 E%, NS), but there was no difference between the groups. However, the total amount of saturated fat was lower (11·2 versus 12·9 E%, $P = 0·04$) and the amount of fiber higher (12·8 versus 11·9 g per 1000 kcal, $P < 0·05$) in the intervention group after 1 year. Fitness index, which is an indirect measure of aerobic capacity from the 2 km walking test, showed significantly greater improvement in the intervention group after 1 year (18 versus 7 units, $P < 0·05$, change in the intervention versus control group, respectively).

## Discussion

After intensive discussion about different strategies to prevent type 2 diabetes in high-risk people, only lifestyle intervention measures were ultimately selected to be applied in the DPS. This decision was based on previous knowledge of the impact of lifestyle factors on the development of type 2 diabetes, and encouraging results from earlier lifestyle intervention studies on IGT patients and newly diagnosed type 2 diabetic patients (Eriksson & Lindgärde, 1991; Laitinen *et al*. 1993; Uusitupa, 1996; Pan *et al*. 1997). It has been shown that even moderate changes in weight, diet composition and physical activity can result in significant improvements in glucose tolerance. Other reasons why we preferred lifestyle intervention only were the lack of an ideal pharmacological agent for this particular purpose, and the less promising experiences from former drug interventions in prevention of diabetes (Uusitupa *et al*. 1997). Finally, the fact that weight loss, healthy diet and increased physical activity are first-line measures to prevent atherosclerotic vascular diseases through several other mechanisms besides the correction of glucose metabolism was an important justification for choosing our intervention strategy.

We used the 2 h OGTT to screen subjects with IGT. This group seems ideal for intervention because they are at high risk not only with respect to type 2 diabetes but also atherosclerotic vascular diseases (Uusitupa *et al*. 1997). In most subjects recruited to the DPS, the IGT diagnosis was based on two OGTTs.

Based on the 1-year data there was a 4·6 kg reduction in mean body weight in the intervention group, while the weight change in the control group was small. Most of the weight loss could be attributed to the loss of fat mass, and not to the loss of lean body mass. Preliminary dietary data indicate that the intervention was successful in reducing the intake of total fat and saturated fatty acids. Furthermore, the improvement in physical fitness index in the intervention subjects suggests that our goal of increasing physical activity in the intervention group was also achieved.

Along with the reduction in excess body weight, a significant improvement was observed in glucose tolerance, blood

pressure and serum triglycerides, and to a lesser extent also in HDL-cholesterol, while serum total cholesterol showed no significant change in the intervention group. These changes, if any, were very small in the control group.

The finding that the most of the weight loss observed after a 1-year intervention was maintained after 2 years in the intervention group is of particular significance. In most weight-reduction programmes (Goldstein & Potvin, 1994), even with the latest pharmacological agents (Sjöström *et al*. 1998), a significant weight regain has been observed 6–12 months after the outset of a programme. The factors contributing to the long-term efficacy of our programme in terms of weight loss include regular visits to intervention centres where the intervention subjects receive continuous support and reinforced counselling, not only with regard to diet and exercise habits, but also other lifestyle factors.

The question as to whether the DPS will be successful in preventing or posponing new cases of type 2 diabetes needs a longer follow-up period. By the end of April 1999 we had confirmed 65 new diabetic cases, 34 drop-outs and one death. The first analysis regarding the difference between the groups in the main outcome measure, i.e. the cumulative incidence of diabetes, will be carried out according to the instructions given by an external expert panel.

In conclusion, these interim results from the ongoing Finnish DPS demonstrate the efficacy and feasibility of the lifestyle intervention programme. If the lifestyle changes observed thus far are permanent, we can assume that the onset of diabetes may be postponed for many years, which would also contribute to a decrease in the progression of atherosclerosis in these high-risk subjects.

## The Finnish Diabetes Prevention Study Group

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