

Long-Term Improvement in Insulin Sensitivity by Changing Lifestyles of People with Impaired Glucose Tolerance

4-Year Results From the Finnish Diabetes Prevention Study

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Lifestyle interventions reduce the incidence of type 2 diabetes among individuals with impaired glucose tolerance (IGT). However, it is unknown whether this is due to improved insulin sensitivity or insulin secretion. We investigated at baseline insulin sensitivity and insulin secretion applying frequently sampled intravenous glucose tolerance test (FSIGT) in 87 of 101 obese middle-aged subjects with IGT randomized into an intervention or a control group in the Finnish Diabetes Prevention Study. FSIGT was repeated after 4 years in 52 people. There were no significant differences in any of the baseline anthropometric or metabolic characteristics between the groups. The 4-year weight and waist circumference decreases were greater in the intervention than in the control group ($P = 0.043$ and $P = 0.025$, respectively). At 4-year examination, insulin sensitivity (S_i) tended to be higher in the intervention group (the difference between the mean values 36%; $P = 0.067$, and $P = 0.136$ after adjustment for age, sex, BMI, and baseline S_i value). There was strong correlation between the 4-year changes in S_i and weight ($r = -0.628$ and $r = -0.710$, for intervention and control groups; $P < 0.001$ for both). In the entire group, S_i improved by 64% in the highest tertile of weight loss but deteriorated by 24% in those who gained weight (lowest tertile). Acute insulin response declined significantly in the control group. In conclusion, S_i markedly improved by weight reduction during the 4-year follow-up of individuals with IGT. Insulin secretion remained constant for years in individuals with IGT who were able to lose weight. *Diabetes* 52:2532–2538, 2003

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AIR, acute insulin response; DPS, Diabetes Prevention Study; FSIGT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; S_g , glucose effectiveness; S_i , insulin sensitivity index.

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Both genetic and environmental factors contribute to the development of type 2 diabetes (1–5). The two major pathogenetic factors involved in disturbed glucose metabolism and ultimately leading to overt diabetes are insulin resistance and impaired β -cell function (6–10). No consensus exists for the relative impact of insulin resistance and impaired insulin secretion on the development of type 2 diabetes, most plausibly because of the heterogeneous nature of type 2 diabetes.

The main environmental risk factors for type 2 diabetes are obesity, in particular the central type of obesity; physical inactivity (1–5); and a high-fat diet, rich in saturated fatty acids (11,12). Low intakes of dietary fiber, whole-grain cereals, and low-glycemic carbohydrates have also been shown to be associated with increased risk (11).

Recent studies indicate that type 2 diabetes is preventable in individuals with impaired glucose tolerance (IGT). Weight reduction, increased physical activity, and changing the diet toward the current recommendations in terms of the quality and quantity of intakes of fat and dietary fiber have been shown to prevent or delay the development of type 2 diabetes by 40–60% in different populations (13–16). However, there are no data from long-term intervention trials concerning the mechanisms that may have resulted in the improved glucose metabolism after lifestyle changes. On the basis of short-term clinical trials, both an improved insulin sensitivity and insulin secretion may play a role in this respect (17–20). We investigated the impact of the 4-year lifestyle intervention on insulin sensitivity and insulin secretion in a group of people who participated in the Finnish Diabetes Prevention Study (DPS) (15) in Kuopio.

RESEARCH DESIGN AND METHODS

General study design of the DPS. The DPS was a randomized, controlled, multicenter study carried out in Finland in 1993–2000. Altogether, 522 subjects with IGT were randomized into either an intervention or a control group in five clinics. The study design and methods used have been reported in detail elsewhere (15,21). The study protocol was approved by the Ethics Committee of the National Public Health Institute in Helsinki, Finland, and all of the study subjects gave written informed consent.

TABLE 1
Baseline characteristics of study participants

	Intervention group	Control group	<i>P</i>	* <i>P</i>	† <i>P</i>
Age (years)	54 ± 8 (52)	53 ± 7 (49)	0.615		
Weight (kg)	86.1 ± 14.2 (52)	87.8 ± 15.7 (49)	0.634	0.945	
BMI (kg/m ²)	30.9 ± 4.0 (52)	31.7 ± 5.0 (49)	0.596	0.740	
Waist circumference (cm)	104.3 ± 10.6 (51)	104.0 ± 10.9 (49)	0.981	0.689	0.134
Fasting glucose (mmol/l)	6.3 ± 0.8 (51)	6.5 ± 0.8 (49)	0.262	0.159	0.182
2-h glucose (mmol/l)	9.1 ± 1.5 (51)	9.3 ± 1.7 (49)	0.612	0.610	0.631
Fasting insulin (pmol/l)	83.5 ± 38.0 (49)	103.6 ± 58.6 (48)	0.134	0.110	0.128
2-h insulin (pmol/l)	616.3 ± 411.6 (38)	632.2 ± 402.0 (36)	0.746	0.726	0.855
HbA _{1c} (%)	5.9 ± 0.9 (50)	5.8 ± 1.0 (47)	0.657	0.681	0.688
AIR (mU · l ⁻¹ · min ⁻¹)	281 ± 286 (47)	259 ± 266 (40)	0.762	0.584	0.585
S _i (×10 ⁻⁴ · min ⁻¹ · μU ⁻¹ · ml ⁻¹)	1.85 ± 1.28 (47)	1.99 ± 1.38 (39)	0.588	0.648	0.632
S _g ([min] ⁻¹ · 10 ²)	1.50 ± 0.51 (47)	1.52 ± 0.48 (40)	0.936	0.841	0.828

Data are mean ± SD (*n*). **P* value after adjustment for age and sex. †*P* value after adjustment for age, sex, and BMI.

The main inclusion criteria were as follows: BMI >25 kg/m², age 40–64 years, and IGT based on the mean values of two oral glucose tolerance tests (OGTTs). Participants with a diagnosis of diabetes and those with a chronic disease rendering survival for 6 years unlikely were excluded from the study. Randomization to the intervention and control groups was stratified according to the clinic, sex, and the mean plasma glucose concentration 2 h after oral glucose load (7.8–9.4 or 9.5–11.0 mmol/l). At baseline and at each annual visits, all study participants completed a medical history questionnaire and underwent a physical examination that included anthropometric and blood pressure measurements and an OGTT, as described earlier in detail (21).

Intervention measures. Briefly, the participants in the intervention group received detailed advice about how to achieve the goals of the intervention, which were a reduction in weight ≥5%, in the total intake of fat <30% of energy, and the intake of saturated fat <10% of energy consumed; an increase in fiber intake to at least 15 g/1,000 kcal; and moderate exercise for at least 30 min per day. Frequent ingestion of fruits, vegetables, whole-grain products, low-fat milk and meat products, soft margarines, and vegetable oils rich in monounsaturated fatty acids was recommended. The dietary advice was tailored to each participant on the basis of 3-day food records completed four times per year. Each participant in the intervention group had seven sessions with a clinical nutritionist during the first year of the study and then one session every 3 months. The intervention participants also received individual guidance on increasing their level of physical activity. Endurance exercise was recommended to improve cardiorespiratory fitness, but also circuit-type resistance training was offered to improve the functional capacity and strength of the large muscles (15).

The control group received general advice about the healthy food and the importance of weight reduction and increasing physical activity for the prevention of type 2 diabetes. If at an annual visit the study physician discovered a clinical condition that required attention, e.g., high serum

cholesterol or high blood pressure, then the participant was advised to contact his or her own physician for the treatment and follow-up.

Four-year study on insulin resistance and insulin secretion. In the Kuopio clinic, in addition to the above-mentioned examinations, at baseline and at the 4-year examination, a frequently sampled intravenous glucose tolerance test (FSIGT) (22) was carried out in all eligible participants who were willing to participate in this study. Eighty-seven participants at baseline and 52 at the 4-year examination participated in the FSIGT. At baseline, 14 subjects (6 intervention and 8 in control group) did not participate in the FSIGT. For five participants, one at baseline and four at the 4-year examination, the insulin sensitivity index (S_i) could not be calculated. The main reasons for dropouts were the development of diabetes during the follow-up (*n* = 21, 8 in intervention and 13 in control group), technical difficulties (*n* = 1, year 0; *n* = 3, year 4), dropout from the main study (*n* = 1, year 0; *n* = 14, year 4), not willing to participate in the FSIGT (*n* = 12, year 0; *n* = 10, year 4), and others (*n* = 3, year 4). Altogether, 15 participants in each group did not participate in the FSIGT at the 4-year examination.

Methods

Anthropometric measurements. BMI was calculated as weight (kg)/height (m²). Waist circumference was measured midway between the lowest rib and the iliac crest, and hip circumference was measured over the great trochanters, with 0.5-cm precision with the participants in a standing position.

Glucose and insulin metabolism. In a 2-h OGTT, samples for glucose and insulin were taken before (0 min) and 120 min after a glucose load (75 g). Plasma glucose was measured locally by standard methods, and the measurements were standardized by the central laboratory in Helsinki (15). Serum insulin was determined with a radioimmunoassay (Pharmacia, Uppsala, Sweden).

FSIGT was performed as previously described (22). First, two intravenous catheters were inserted in the antecubital veins on both arms and the fasting

TABLE 2
Baseline characteristics and the 4-year weight change in participants who developed or did not develop type 2 diabetes during the 4-year follow-up

	Type 2 diabetes at 4-year	No type 2 diabetes at 4-year	<i>P</i> value	* <i>P</i>	† <i>P</i>
Age (years)	55 ± 6 (21)	54 ± 7 (68)	0.692		
Weight (kg)	96.3 ± 18.0 (21)	84.4 ± 12.9 (68)	0.003	0.002	
BMI (kg/m ²)	34.1 ± 5.8 (21)	30.4 ± 3.9 (68)	0.007	0.001	
Waist circumference (cm)	111.7 ± 12.7 (21)	101.7 ± 9.1 (68)	0.001	<0.001	0.099
Weight change (kg)‡	0.5 ± 4.3 (21)	-2.8 ± 5.5 (67)	0.016	0.015	0.034
Fasting glucose (mmol/l)	7.0 ± 0.8 (21)	6.2 ± 0.7 (68)	<0.001	<0.001	0.001
2-h glucose (mmol/l)	10.2 ± 1.4 (21)	8.8 ± 1.5 (68)	<0.001	<0.001	0.001
Fasting insulin (pmol/l)	111.8 ± 64.2 (19)	86.7 ± 44.1 (66)	0.123	0.095	0.906
2-h insulin (pmol/l)	626.8 ± 410.7 (17)	620.6 ± 409.2 (48)	0.805	0.706	0.441
HbA _{1c} (%)	6.0 ± 1.0 (21)	5.8 ± 1.0 (65)	0.288	0.353	0.277
AIR (mU · l ⁻¹ · min ⁻¹)	108 ± 106 (18)	307 ± 287 (61)	<0.001	<0.001	<0.001
S _i (×10 ⁻⁴ · min ⁻¹ · μU ⁻¹ · ml ⁻¹)	1.54 ± 1.09 (17)	2.05 ± 1.27 (61)	0.145	0.107	0.896
S _g ([min] ⁻¹ · 10 ²)	1.34 ± 0.35 (18)	1.58 ± 0.52 (61)	0.048	0.113	0.272

Data are mean ± SD (*n*). **P* value after adjustment for age and sex. †*P* value after adjustment for age, sex, and BMI. ‡In patients with type 2 diabetes, the baseline weight was subtracted from the weight measured at the visit when type 2 diabetes diagnosis was done. In participants who did not have type 2 diabetes at the 4-year examination, the baseline weight was subtracted from the weight measured at the 4-year visit.

TABLE 3
Baseline and 4-year follow-up data and 4-year changes in anthropometric and metabolic values in participants who participated in repeated FSIGT examination

	Intervention group			Control group						
	Baseline*	4-year	Change	n	‡P	Baseline	4-year	Change	n	‡P
Age (years)	56 ± 7	79.6 ± 15.8	-4.9 ± 4.9‡§	31	<0.001	55 ± 7	83.5 ± 14.3	-1.4 ± 5.5	21	<0.001
Weight (kg)	84.6 ± 13.9	28.6 ± 4.4	-1.8 ± 1.9‡	31	<0.001	84.9 ± 14.2	30.0 ± 3.9	-0.5 ± 2.0	21	0.227
BMI (kg/m ²)	30.4 ± 3.9	98.1 ± 12.2	-4.2 ± 5.2‡	31	<0.001	30.5 ± 4.1	99.9 ± 7.8	-1.8 ± 4.5	20	0.096
Waist circumference (cm)	102.3 ± 11.0	6.3 ± 0.8	0.08 ± 0.73	31	0.557	102.0 ± 8.3	6.3 ± 0.7	0.10 ± 0.75	21	0.537
Fasting glucose (mmol/l)	6.2 ± 0.8	9.2 ± 2.8	0.39 ± 3.09	31	0.544	6.2 ± 0.6	8.9 ± 1.5	0.23 ± 2.38	21	0.659
2-h glucose (mmol/l)	8.8 ± 1.6	68.9 ± 38.7	-15.4 ± 27.0	29	0.001	8.6 ± 1.5	77.7 ± 29.3	-25.7 ± 60.3	20	0.086
Fasting insulin (pmol/l)	78.0 ± 36.3	441 ± 290	-168 ± 417	19	0.152	103.1 ± 57.6	510 ± 276	-68 ± 378	15	0.344
2-h insulin (pmol/l)	577 ± 405	5.8 ± 0.5	-0.11 ± 0.99	30	0.559	556 ± 332	5.9 ± 0.5	0.14 ± 0.95	20	0.531
HbA _{1c} (%)	5.9 ± 0.9	244 ± 245	-27 ± 162	31	0.281	5.8 ± 0.9	270 ± 210	-66 ± 107	21	0.011
AIR (mU · l ⁻¹ · min ⁻¹)	272 ± 299	2.64 ± 1.44	0.34 ± 1.46	28	0.227	336 ± 284	1.94 ± 0.95	0.16 ± 0.96	20	0.474
S _i (×10 ⁻⁴ · min ⁻¹ · μU ⁻¹ · ml ⁻¹)	2.13 ± 1.37	1.54 ± 0.50	0.05 ± 0.69	29	0.683	1.91 ± 1.12	1.34 ± 0.43	-0.32 ± 0.63	20	0.036
S _g ([min] ⁻¹ · 10 ²)	1.50 ± 0.54					1.66 ± 0.46				

Data are mean ± SD. *There were no significant differences in any of the baseline variables between the intervention and control groups. †P value within the study group change. ‡P < 0.05 between the study groups. §P = 0.043 for the change in weight and P = 0.025 for the change in waist circumference, adjusted for age and sex, between the study groups when all participants with follow-up data are included (n = 39 for intervention and n = 29 for control group).

samples were drawn. Glucose dose of 300 mg/kg body wt was given intravenously as a 50% solution in 1.5 min followed by 10 ml of 0.9% NaCl solution. Thereafter, a 0.9% NaCl solution was slowly infused until a bolus of 0.03 units/kg insulin was rapidly injected 20 min after the glucose dose. NaCl infusion was continued for 1.5 min after the insulin dose. For determining plasma glucose and insulin levels, venous blood samples were collected before the glucose dose (-5 and 0 min) and 23 times after the glucose dose (at 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 24, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 min) via a catheter in the contralateral arm. For arterializing venous blood, the arm was kept in a 50°C electric pad during the test. Plasma glucose concentration was analyzed by a glucose oxidase method (Glucose Auto & Stat, Model GA-110; Daiichi, Kyoto, Japan) and plasma insulin by a radioimmunoassay method (Phadaseph Insulin RIA 100; Pharmacia Diagnostica, Uppsala, Sweden). The data were analyzed by calculating glucose effectiveness (S_g) and S_i with the Minmod program (23). In addition, the acute insulin response (AIR) was determined by calculating the area under the insulin curve above the baseline level from 0 to 10 min.

Statistical analysis. Statistical analyses were performed using the SPSS/WIN program version 11.0 (SPSS, Chicago, IL). Normal distribution of continuous variables was checked with the Kolmogorov-Smirnov test with Lilliefors correction, and logarithmic transformation was used for those variables that were not normally distributed. The differences between the study groups or between participants who developed or did not develop type 2 diabetes during the 4-year follow-up were evaluated by the univariate ANOVA (general linear model) adjusting for age, sex, BMI, and baseline S_i value (4-year results), when appropriate. Multiple regression analyses were used to assess the factors predicting the changes in the S_i, the acute insulin response, the fasting insulin, and the 2-h insulin. In the regression analyses, study groups were encoded as 1 = intervention group and 2 = control group, and the weight change was calculated as (weight [kg]_{4 year} - weight [kg]_{baseline})/weight [kg]_{baseline} × 100. Spearman's nonparametric correlation analysis was used for the assessment of association between the changes in the insulin sensitivity index, AIR, and body weight. Also, paired and unpaired t tests were used when applicable. P < 0.05 was considered statistically significant. Data are presented as mean ± SDs, unless otherwise indicated.

RESULTS

Baseline characteristics by group. Table 1 shows the baseline clinical characteristics by the original randomization group. The mean age of the participants was 54 years in the intervention group and 53 years in the control group. There were no significant differences in anthropometric variables, fasting or 2-h glucose, and insulin levels. Also AIR, S_i, and S_g were comparable between the intervention and control subjects.

Anthropometric and metabolic characteristics at baseline and body weight change in relation to the diabetes risk. Altogether, 21 participants (8 in the intervention and 13 in the control group) developed diabetes during the 4-year follow-up (Table 2). Participants who developed diabetes were heavier at baseline, and they had larger waist circumference; in addition, they were less able to reduce their body weight than participants who remained nondiabetic at the 4-year examination. The initial fasting and 2-h glucose values were higher and AIR was more impaired in participants who developed diabetes than in those who did not. There was no significant difference in S_i at baseline between the participants with and without diabetes after 4 years, but S_g was significantly lower in those who later developed diabetes.

Four-year changes in anthropometric and metabolic characteristics by group. The 4-year changes in anthropometric and metabolic values in participants who participated in repeated FSIGT examination are summarized in Table 3. Participants with incident diabetes were excluded, because their follow-up was discontinued after receiving a diagnosis of having diabetes according to the study design. The 4-year weight reduction was larger in the intervention than in the control group. Similarly, waist

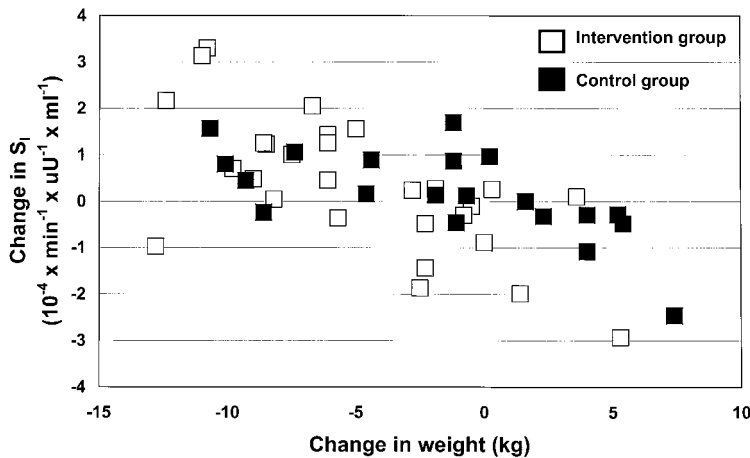


FIG. 1. The Spearman's nonparametric correlations between the changes in the S_1 and body weight in the intervention group ($r = -0.628$, $P < 0.001$, $n = 28$) and in the control group ($r = -0.710$, $P < 0.001$, $n = 20$).

circumference reduced more in the intervention group. Fasting insulin level decreased significantly only in the intervention group. There were no statistically significant differences between randomization groups in the changes of fasting or 2-h glucose values or in fasting and 2-h insulin levels. It is interesting that AIR declined significantly only in the control group, whereas the declining tendency was small in the intervention group. S_1 , however, was numerically higher ($P = 0.227$) at the 4-year follow-up than at baseline in the intervention group, whereas it remained unchanged in the control group. S_g decreased in the control group but remained unchanged in the intervention group. However, there were no significant differences in the changes in AIR or S_1 between the groups. The difference in the changes in S_g was close to the statistical significance ($P = 0.062$). It is worth noting that the variations in the changes of S_1 and AIR in both the intervention and control groups were large. At the 4-year examination, S_1 tended to be higher in the intervention group than in the control group (the difference between the mean values 36%; $P = 0.067$, and $P = 0.136$ after adjustment for age, BMI, sex, and baseline S_1 value).

Correlations between the changes in body weight and insulin sensitivity, insulin secretion, and fasting and 2-h insulin in the entire study group. Figure 1 shows the correlation between the changes in body weight and S_1 in the entire cohort. The change in S_1 strongly correlated with the change in body weight. In participants with weight loss of 8–17.2% (1st tertile), S_1 improved by 64%, whereas in those with an increase in body weight, S_1

decreased by 24% (3rd tertile, weight change -1.4 to 10.0% ; Fig. 2).

We also analyzed the factors associated with changes in S_1 , AIR, and fasting and 2-h insulin levels adjusting for confounding effects by multiple regression analyses (Table 4). Factors were selected for analyses on the basis of the results of univariate analyses and their plausible biological relevance. Weight change was the only factor that had a significant contribution to the improvement in S_1 , and it was also associated with a decrease in both fasting and 2-h insulin levels during the 4-year follow-up. None of the variables examined was related to the changes in AIR. We also carried out multiple regression analysis (Table 4) after excluding S_1 change, but this did not change the results. In Spearman correlation analysis, there was a weak inverse correlation between the changes in body weight and AIR ($r = -0.239$, $P = 0.087$, $n = 52$). The percentage changes in AIR by tertiles of weight loss were -1.3 , 5.4 , and -14.6% in the 1st (-17.2 to -8.0%), 2nd (-7.9 to -1.0%), and 3rd (-0.9 to 9.7%) tertiles ($n = 52$). Thus, insulin secretion remained constant for 4 years in IGT participants who were able to lose weight. An improvement in S_1 was not correlated with AIR ($r = -0.08$, $P = 0.589$).

DISCUSSION

Recent studies have shown that lifestyle changes are effective in preventing or delaying the development of type 2 diabetes (13–16). In principle, two main reasons have

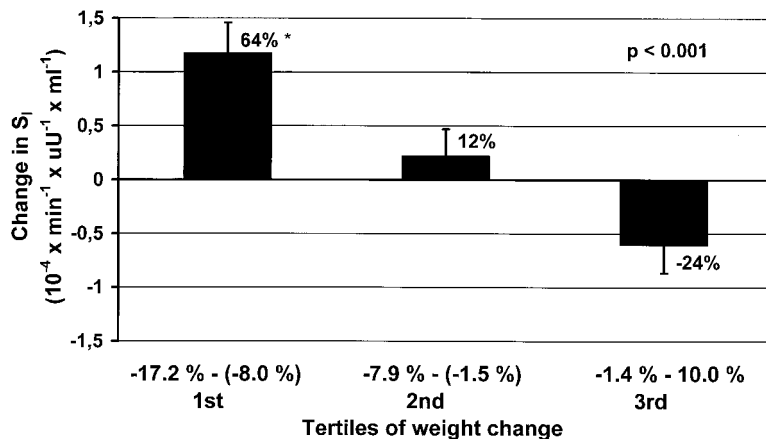


FIG. 2. The changes in the S_1 by tertiles ($n = 16$ in each tertile) of 4-year body weight change (mean \pm SE), both groups combined. The P value indicates the significance of the difference among the tertiles after adjustment for age, sex, and study group. *The percentage change in the group mean.

TABLE 4

Regression analyses for the changes of the S_i , the acute insulin response, the fasting insulin, and the 2-h insulin

	Regression coefficient	<i>P</i> value
Change in the S_i ($n = 48$)		
Baseline weight	0.10	0.920
Age	0.37	0.847
Sex	-0.62	0.982
Study group*	7.46	0.769
Weight change (%)†	-8.10	<0.001
Change in AIR ($\text{mU} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$)	-0.15	0.077
Change in the acute insulin response ($n = 48$)		
Baseline weight	0.23	0.730
Age	-1.07	0.408
Sex	0.22	0.990
Study group*	-7.70	0.659
Weight change (%)†	-3.22	0.083
Change in S_i ($\times 10^{-4} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$)	-10.02	0.254
Change in the fasting insulin ($n = 66$)		
Baseline weight	-0.93	0.061
Age	-1.57	0.065
Sex	4.29	0.731
Study group*	-10.26	0.388
Weight change (%)†	5.01	<0.001
Change in the 2-h insulin ($n = 47$)		
Baseline weight	-0.93	0.221
Age	0.24	0.853
Sex	-12.98	0.542
Study group*	-8.01	0.679
Weight change (%)†	3.89	0.012

*Study groups were encoded as 1 = intervention group and 2 = control group. †Weight change was calculated as $\{[\text{weight (kg)}_{4 \text{ year}} - \text{weight (kg)}_{\text{baseline}}] / [\text{weight (kg)}_{\text{baseline}}]\} \times 100$.

been suggested to be responsible for worsening of impaired glucose metabolism, ultimately resulting in overt diabetes: progressive insulin resistance and impairment in insulin secretion (6–10). It has been generally accepted that in most cases of type 2 diabetes, both of these mechanisms need to be operative, but their relative contribution may vary depending on both environmental and genetic factors (24). Our results show that a sustained weight reduction in participants with IGT resulted in a substantial improvement in insulin sensitivity measured by S_i . More people developed diabetes in the control group than in the intervention group. Because these people were excluded from the 4-year analyses, there is a bias the magnitude of which is difficult to estimate.

Our 4-year results indicate that in patients with IGT, the changes in insulin resistance are strongly correlated with the changes in body weight. A further weight gain is detrimental in terms of insulin resistance, but weight reduction improves insulin sensitivity substantially, and the improvement is dependent on the degree of weight loss (Fig. 2). This is also in line with what we know about the impact of the main risk factors, obesity and sedentary lifestyle, on causes of disturbed glucose tolerance; both obesity and physical inactivity increase insulin resistance. Furthermore, numerous short-term studies have shown that it is possible to improve insulin action and to diminish hepatic glucose production by weight loss and increasing physical activity in different degrees of disturbances of glucose metabolism, including patients with type 2 diabetes (17–21,25–28). In some studies in patients with type 2 diabetes, insulin secretion also has been found to be improved after weight loss (18). An improved metabolic

control in patients with recently diagnosed type 2 diabetes has been shown to be associated with weight reduction, initially high fasting insulin reflecting insulin resistance, and improved insulin secretion (27,29,30). Increased physical activity (25,26,28,31) and changes in the quality of dietary fat (12) could also contribute to an improved insulin sensitivity observed in the intervention group of the present study, and they may also partly explain the remarkable reduction in the incidence of diabetes in the main DPS (15).

Recent studies have increased our understanding about the basic mechanisms explaining insulin resistance in obesity. The main functional defects, decreased insulin-stimulated glucose transport and metabolism in muscle and fat tissue and impaired suppression of hepatic glucose output, can be attributed to impaired insulin signaling in these tissues (32,33). An increased release and concentration of free fatty acids has been suggested to cause insulin resistance and inhibit insulin clearance, but high insulin levels per se could also result in insulin resistance. Insulin resistance could also be related to skeletal muscle triglyceride content or the fatty acid composition of cell membranes (34–36). Weight reduction and physical activity, through several mechanisms, could, therefore, result in an improved insulin sensitivity (34–37).

First-phase defect in insulin secretion has been shown to predict the development of type 2 diabetes among individuals with impaired glucose metabolism (8,9), even independent of obesity and insulin resistance. However, insulin resistance and insulin secretion may be connected with each other, e.g., through lipotoxicity or glucotoxicity (38–41). In the present study, participants who developed

diabetes during the 4-year follow-up were initially more obese and they could not lose weight, but they already had higher fasting and 2-h glucose values and more impaired insulin secretion based on AIR. This suggests that in them, the impairment in insulin secretion in conjunction with documented insulin resistance could mainly explain the development of diabetes.

Among participants who did not develop diabetes, AIR declined in the control group but remained almost unchanged in the intervention group. Furthermore, the change in AIR was weakly related to the change in body weight but not to the change in insulin sensitivity. Thus, we cannot exclude the possibility that weight reduction per se or other dietary or lifestyle changes could also have an impact on preserved insulin secretion capacity (32). However, on the basis of the present results, an improved insulin sensitivity may largely explain the substantial reduction in the incidence of diabetes in the main DPS (15).

The present study participants represented only ~20% of all DPS study subjects, and because of development of diabetes and dropouts, only 52 of them passed the 4-year FSIGT study. On the basis of the available data, there were no significant differences in baseline characteristics of this subsample of subjects (data not shown) compared with those who did not participate in the FSIGT or the entire study population of DPS (15), suggesting no bias in this respect. Unfortunately, we did not examine AIR or S_i in people with incident diabetes during the follow-up. FSIGT is a suitable method to examine insulin sensitivity and secretion in subjects with disturbed glucose metabolism, including those with IGT, but the validity of this method has been questioned in overt diabetes (42).

The present results show that it is possible to achieve a sustained improvement in insulin sensitivity by moderate weight loss and healthy lifestyles. The improvement in insulin sensitivity is strongly related to the degree of weight reduction and could largely explain why the lifestyle interventions are successful in the prevention of type 2 diabetes. This view is supported by the findings from observational studies on different ethnic groups (43) and that most overweight subjects with IGT are insulin-resistant. It is interesting that weight reduction could also have a weak impact on insulin secretion, but this view needs to be confirmed in further studies. Finally, changing lifestyles also correct cardiovascular risk factors in individuals with IGT (44).

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REFERENCES

1. Neel JV: Diabetes mellitus: a thrifty genotype rendered detrimental by progress. *Am J Human Genet* 14:353–362, 1960
2. Tuomilehto J, Wolf E: Primary prevention of diabetes mellitus. *Diabetes Care* 10:238–248, 1987
3. King H, Dowd JE: Primary prevention of type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 33:3–8, 1990
4. Hamman RF: Genetic and environmental determinants of non-insulin-dependent diabetes mellitus (NIDDM). *Diabetes Metab Rev* 8:287–338, 1992
5. Zimmet PZ: Primary prevention of diabetes mellitus. *Diabetes Care* 11:258–262, 1988
6. Gerich JE: Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes. *Diabetes* 51 (Suppl. 1):S117–S121, 2002
7. Bergman RN, Ader M, Huecking K, Van Citters G: Accurate assessment of beta-cell function. The hyperbolic correction. *Diabetes* 51 (Suppl. 1):S212–S220, 2002
8. Bogardus C, Tataranni A: Reduced early insulin secretion in the etiology of type 2 diabetes mellitus in Pima Indians. *Diabetes* 51 (Suppl. 1):S262–S264, 2002
9. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992, 1993
10. Cerasi E: Insulin deficiency and insulin resistance in the pathogenesis of type 2 diabetes: is a divorce possible? *Diabetologia* 38:992–997, 1995
11. Hu FB, van Dam RM, Liu S: Diet and risk of type 2 diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44:805–817, 2001
12. Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell L, Nalsen G, Berglund L, Louheranta A, Rasmussen BM, Calveret GD, Maffione A, Pedersen E, Gustafsson IB, Storlien LH: Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU-Study. *Diabetologia* 44:312–319, 2001
13. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmo feasibility study. *Diabetologia* 34:891–898, 1991
14. Pan X, Li G, Hu Y, Wang J, Yang W, An Z, Hu Z, Lin J, Xiao J, Cao H, Liu P, Jiang X, Jiang Y, Wang J, Zheng H, Zhang H, Bennett P, Howard B: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
15. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, for the Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
16. Knowler WC, Barrett-Connor E, Fowler SE, Hamman S, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
17. Nagulesparan M, Savage PJ, Bennion LJ, Unger RH, Bennett PH: Diminished effect of caloric restriction on control of hyperglycemia with increasing known duration of type II diabetes mellitus. *J Clin Endocrinol Metab* 53:560–568, 1981
18. Henry RR, Wallace P, Olefsky JM: Effects of weight loss on mechanism of hyperglycemia in obese non-insulin-dependent diabetes mellitus. *Diabetes* 35:990–998, 1986
19. Wing R, Koeske R, Ebstein LH, Nowalk MP, Gooding W, Becker D: Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med* 147:1749–1953, 1987
20. Laakso M, Uusitupa M, Takala J, Majander H, Reijonen T, Penttilä I: Effects of hypocaloric diet and insulin therapy on metabolic control and mechanisms of hyperglycemia in obese non-insulin-dependent diabetic subjects. *Metabolism* 37:1092–1100, 1988
21. Eriksson J, Lindström J, Valle T, Aunola S, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Lauhkonen M, Lehto P, Lehtonen A, Louheranta A, Mannelin M, Martikkala V, Rastas M, Sundvall J, Turpeinen A, Viljanen T, Uusitupa M, Tuomilehto J: Prevention of type II diabetes in subjects with impaired glucose tolerance: the Diabetes Prevention Study (DPS) in Finland: study design and 1-year interim report on the feasibility of the lifestyle intervention programme. *Diabetologia* 42:793–801, 1999
22. Bergman R: Toward physiological understanding of glucose tolerance. Minimal model approach. *Diabetes* 38:1512–1527, 1989
23. Pacini G, Bergman RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsiveness from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed* 23:112–122, 1986
24. Vauhkonen I, Niskanen L, Vanninen E, Kainulainen S, Uusitupa M, Laakso M: Defects in insulin secretion and insulin action in non-insulin-dependent diabetes mellitus are inherited: metabolic studies on offspring of diabetic probands. *J Clin Invest* 101:86–96, 1998
25. Ross R, Dagnone D, Jones P, Smith H, Paddags A, Hudson R, Janssen I: Reduction in obesity and related comorbid conditions after diet-induced

- weight loss or exercise induced weight loss in men. A randomised, controlled trial. *Ann Intern Med* 133:92–103, 2000
26. Borghouts LB, Keizer HA: Exercise and insulin sensitivity. *Int J Sports Med* 21:1–12, 2000
 27. Laitinen J, Uusitupa M, Ahola I, Laakso M, Siitonen O: Metabolic and dietary variables associated with glycemic control in patients with recently diagnosed type II diabetes mellitus. *Diabetes Nutr Metab* 7:77–87, 1994
 28. Ryan AS: Insulin resistance with aging: effects of diet and exercise. *Sports Med* 30:327–346, 2000
 29. Uusitupa M, Laitinen J, Siitonen O, Vanninen E, Pyörälä K: The maintenance of improved metabolic control after intensified diet therapy in recent type 2 diabetes. *Diabetes Res Clin Pract* 19:227–238, 1997
 30. Uusitupa M: Early lifestyle intervention in patients with non-insulin-dependent diabetes mellitus and impaired glucose tolerance. *Ann Med* 28:445–449, 1996
 31. Wei M, Gibbons L, Mitchell TL, Kampert JB, Lee CL, Blair SN: The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes in men. *Ann Intern Med* 130:89–96, 1999
 32. Kahn B, Flier JS: Obesity and insulin resistance. *J Clin Invest* 106:473–481, 2000
 33. Reaven GM: Pathophysiology of insulin resistance in human disease. *Physiol Rev* 75:473–486, 1995
 34. Frayn KN: Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 45:1201–1210, 2002
 35. Houmard JA, Tanner CJ, Yu C, Cunningham PG, Pories WJ, MacDonald KG, Shulman GI: Effect of weight loss on insulin sensitivity and intramuscular long-chain fatty acyl-Coas in morbidly obese subjects. *Diabetes* 51:2959–2963, 2000
 36. Frayn KN: Visceral fat and insulin resistance—causative or correlative. *Br J Nutr* 83 (Suppl. 1):S71–S77: 2000
 37. Zierath JR, Krook A, Wallberg-Henriksson H: Insulin action and insulin resistance in human skeletal muscle. *Diabetologia* 43:821–835, 2000
 38. Unger RH, Zhou Y-T: Lipotoxicity of beta-cells in obesity and in other causes of fatty acid spillover. *Diabetes* 50 (Suppl. 1):S118–S121, 2001
 39. Weir GC, Ross Laybutt D, Kaneto H, Bonner-Weir S, Sharma A: Beta-cell adaptation and decompensation during the progression of diabetes. *Diabetes* 50 (Suppl. 1):S154–S159, 2001
 40. Bernard-Kargar C, Ktorza A: Endocrine pancreas plasticity under physiological and pathological conditions. *Diabetes* 50 (Suppl. 1):S30–S35, 2001
 41. Porte D Jr, Kahn SE: Beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 50 (Suppl. 1):S160–S163, 2001
 42. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ Bergman RN: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Insulin Resistance Atherosclerosis Study. *Diabetes* 43:1114–1121, 1994
 43. Haffner SM, Mykkänen L, Festa A, Burke JP, Stern MP: Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects. *Circulation* 101:975–980, 2000
 44. Uusitupa M: Lifestyle matter in the prevention of type 2 diabetes. *Diabetes Care* 25:1650–1651, 2002