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Improved fibrinolysis by an intensive lifestyle intervention in subjects with impaired glucose tolerance. The Finnish Diabetes Prevention Study

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Abstract *Aims/hypothesis:* The aim of this study was to investigate the effects of lifestyle intervention on the levels

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of plasminogen activator inhibitor (PAI-1) and fibrinogen in subjects participating in the Finnish Diabetes Prevention Study (DPS). *Methods:* In five DPS centres, 321 subjects with impaired glucose tolerance (intervention group, $n=163$; control group, $n=158$) had their PAI-1 and fibrinogen levels measured at baseline and at the 1-year follow-up. Additional 3-year follow-up assessments were carried out in a sample of 97 subjects in one of the DPS centres (Turku). The intervention programme included an intensive lifestyle intervention aiming at weight reduction, healthy diet and increased physical activity. *Results:* During the first intervention year, PAI-1 decreased by 31% in the intervention group but showed no change in the control group ($p<0.0001$). In the Turku subgroup, the decrease in PAI-1 persisted throughout the 3-year follow-up. Changes in PAI-1 were associated with the number of lifestyle changes made during the first year ($p=0.008$). Weight reduction was the most important factor explaining the decrease in PAI-1. Changes in fibrinogen levels did not differ between the groups. *Conclusions/interpretation:* In addition to the previously reported reduction in the risk of type 2 diabetes in DPS participants with impaired glucose tolerance, the intensive dietary and exercise intervention had beneficial long-term effects on fibrinolysis as indicated by the reduced levels of PAI-1. These results suggest that elevated PAI-1 levels in obese subjects with impaired glucose tolerance are mostly reversible by lifestyle changes, especially those geared to weight reduction.

Keywords Diet · DPS · Fibrinogen · Impaired glucose tolerance · Lifestyle · Physical activity · Plasminogen activator inhibitor · Weight

Abbreviations DPS: Diabetes Prevention Study · E%: per cent of total energy intake · HOMA-IR: homeostasis model assessment for insulin resistance · LTPA: leisure-time physical activity · PAI-1: plasminogen activator inhibitor-1 · WHO: World Health Organization

Introduction

Subjects with type 2 diabetes have an increased risk of atherosclerotic and thrombotic complications, leading to increased morbidity and mortality from CHD or cerebrovascular and peripheral vascular diseases [1, 2]. Even subjects with milder disturbances in glucose metabolism, such as IGT, are at an increased risk of cardiovascular disease [3, 4].

Several studies have shown that high plasma fibrinogen levels represent an independent marker for cardiovascular morbidity in both non-diabetic [5] and diabetic [6] subjects. Diabetic subjects have higher fibrinogen levels than the general population [7], but the data on subjects with IGT are contradictory [8, 9]. Plasminogen activator inhibitor (PAI-1) is a fast-acting inhibitor of fibrinolysis. It has been proposed that decreased fibrinolytic activity and increased circulating PAI-1 play a role in thrombosis/fibrinolysis and contribute to the development of cardiovascular disease in the metabolic syndrome and type 2 diabetes [10]. Some, but not all, studies have reported raised PAI-1 levels in subjects with IGT [11, 12]. A high PAI-1 level may also be a predictor for the development of type 2 diabetes [13, 14].

The effects of physical activity on PAI-1 and fibrinogen levels in healthy subjects are contradictory [15, 16]. Weight reduction has been associated with reductions in both PAI-1 [17, 18] and fibrinogen [17] in obese subjects. A weight-reducing diet combined with exercise has had beneficial effects on fibrinolysis in subjects with or without glucose intolerance over a period of 1 year in some [19, 20] but not all [21] studies. However, there are no studies with long-term follow-up.

The Finnish Diabetes Prevention Study (DPS) showed that intensive lifestyle intervention reduced the risk of type 2 diabetes by 58% in IGT subjects [22]. This analysis aimed both to evaluate the effects of this intervention on changes in PAI-1 and fibrinogen during the first year of the intervention and to determine whether these changes persisted during the subsequent years.

Subjects and methods

Subjects and study design The DPS was a randomised, controlled study carried out in five study centres in Finland from 1993 to 2000. The study design and methods have been described in detail elsewhere [22–24]. In brief, a total of 522 subjects with IGT were randomised into either a lifestyle intervention group or a control group receiving the usual care. The inclusion criteria were as follows: overweight (BMI > 25 kg/m²), age 40–64 years at randomisation, and IGT according to the World Health Organization (WHO) 1985 criteria [25]. The subjects were randomly assigned to one of the two treatment modalities, the intensive lifestyle intervention group or a control group. The intervention aimed at weight reduction, increased physical activity and a low-saturated-fat, high-fibre diet. The study was approved by the ethics committee of the National

Public Health Institute in Helsinki, Finland. All participants gave written informed consent.

Of the DPS participants, 321 subjects (intervention group, $n=163$; control group, $n=158$) had blood drawn and plasma stored for the analysis of PAI-1 and fibrinogen at baseline and at the 1-year follow-up. These subjects were from all five centres. However, because some of the centres recruiting study subjects did not initially include plasma sampling for PAI-1 and fibrinogen in their study protocol, the number of subjects with blood specimens is less than the total number of subjects in the entire DPS. In one study centre (Turku) the haemostatic variables were also analysed at the 3-year follow-up. Of the original 110 subjects in that study group (intervention, $n=55$; control, $n=55$), 15 subjects developed diabetes during the first or second year and did not attend the 3-year follow-up and four subjects dropped out; thus, 91 subjects (intervention, $n=49$, control, $n=42$) formed the study population at the 3-year follow-up.

Data collection At baseline and at each annual visit, blood samples were drawn in the morning after a minimum of 10 h fasting. All subjects underwent a 2-h 75-g OGTT, their medical history and nutrient intake were recorded, and physical examinations were performed [23]. The nutrient intakes were calculated from 3-day food diaries using a program developed at the National Public Health Institute [26]. Leisure-time physical activity (LTPA) was assessed as described earlier [24, 27, 28]. The goals of lifestyle changes during the first year (weight reduction $\geq 5\%$, physical activity with moderate intensity ≥ 30 min/day, dietary fat <30% of total energy intake [E%], saturated fat <10 E%, and fibre ≥ 15 g/1000 kcal) were summed up as a success score, as reported earlier [22].

Biochemical assessments Methods for the determination of glucose, HbA_{1c}, insulin and serum lipids have been described previously [23]. Insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) method as previously described [(fasting insulin in mU/l $\times$ fasting glucose in mmol/l)/22.5] [29]. Blood for haemostatic assessments was drawn after the other specimens with minimal stasis. The samples were centrifuged immediately. Plasma was collected and immediately frozen and stored at -70°C . Plasma fibrinogen was measured by liquid-phase immunoprecipitation assay with nephelometric end-point detection (Turbox Fibrinogen Assay, Orion Diagnostica, Espoo, Finland). Intra-assay variation was 2.0% and inter-assay variation was 4.9% at the 3.8 g/l level. PAI-1 activity was assessed by a chromogenic method based on two-stage, indirect enzymatic assay (Spectrolyse/pL PAI; Biopool International, Ventura, CA, USA). Intra-assay variations were 2.8% at the 17.5 U/ml level and 2.3% at the 28.7 U/ml level. The corresponding inter-assay variations were 4.8% and 8.6%. Fibrinogen and PAI-1 levels were analysed in the laboratory of the Research Department of the Social Insurance Institution.

Table 1 Baseline characteristics

	Intervention	Control
Number of subjects (men/women)	163 (53/110)	158 (49/109)
Age (years)	55.6±7.0	54.8±6.7
Weight (kg)	86.7±13.3	86.9±15.0
BMI (kg/m ²)	31.2±4.2	31.4±4.6
Fasting plasma glucose (mmol/l)	6.27±0.75	6.25±0.66
2-h plasma glucose (mmol/l)	8.98±1.53	8.95±1.46
Fasting serum insulin (mU/l)	15.2±7.9	15.1±7.9
2-h serum insulin (mU/l)	97.1±69.3	92.4±54.5
HbA _{1c} (%)	5.67±0.55	5.57±0.59
HOMA-IR	4.32±2.41	4.27±2.49
PAI-1 (U/ml)	30.8±23.8	29.7±19.7
Fibrinogen (g/l)	4.03±0.81	3.98±0.73
Dietary fat (E%)	34.9±6.6	37.0±6.5 ^a
Saturated fat (E%)	15.7±4.1	17.1±4.2 ^b
Dietary fibre (g/1000 kcal)	11.9±4.0	11.8±4.2
Moderate to vigorous LTPA (min/week)	161±159	153±183

Data are given as mean±SD

^a*p*=0.005, ^b*p*=0.003 between groups

Statistical analysis Two-sided Student's *t*-test or the non-parametric Wilcoxon's signed-rank test was used to analyse the differences between the intervention and control groups. The changes in variables were analysed using a general linear mixed model with repeated measures. Logarithmic or square-root transformations were applied, if necessary. The validity of the models was evaluated with residual analysis. If the validity of the models was not fulfilled, Wilcoxon's signed-rank test was applied. Untransformed data are presented in the tables. Group and centre were included in the model as the between-subjects factors and time as the within-subject factor. Mean changes in both groups were assessed by contrast with the 95% confidence intervals, regardless of whether or not the group×time interaction was significant. The association between PAI-1 and the other factors was tested with re-

peated ANOVA defining weight, HbA_{1c}, 2-h glucose, HOMA-IR, dietary fat as E%, saturated fat as E%, intake of dietary fibre, and moderate to vigorous LTPA as time-dependent covariates, and group as a between-subjects factor. *R*² values for changes between PAI-1 and independent variables were calculated separately by regression analysis. The linear trend in success score and PAI-1 changes was tested by one-way ANOVA. All statistical analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC, USA). Statistical significance was taken as a *p* value of 0.05 or less.

Results

The 321 subjects with haemostatic measurements did not differ from the rest of the study population (*n*=201), except for fasting glucose (6.26±0.71 mmol/l vs 5.94±0.77 mmol/l, *p*<0.0001). The differences in baseline characteristics between the subjects in the intervention group and the control group were not significant, except for the dietary fat and saturated fat intakes, which were higher in the control group (Table 1).

During the first year, the weight reduction was 4.7 kg (5%) in the intervention group, compared with 1.1 kg (1%) in the control group (*p*<0.0001) (Table 2). The intake of dietary and saturated fat as E% decreased in both groups, but the intake of saturated fat decreased by a significantly greater degree in the intervention group (19% vs 9%, *p*=0.01). Subjects in the intervention group increased their intake of dietary fibre by a significantly greater amount than control subjects (*p*<0.0001). Moderate to vigorous LTPA increased markedly in the intervention group (25%, *p*<0.0005), but only slightly in the control group (4%, *p*=0.02). HbA_{1c} and fasting glucose decreased in the intervention group (1% and 5%, respectively) while in the control group HbA_{1c} increased by 3% and fasting glucose did not change. The decreases in 2-h glucose, fasting insulin and 2-h insulin were also larger in the intervention group.

Table 2 Changes in weight, metabolic and lifestyle variables from baseline to 1-year follow-up

	Intervention group (<i>n</i> =163)		Control group (<i>n</i> =158)		<i>p</i> value ^a
	Mean	95% CI	Mean	95% CI	
Weight (kg)	-4.7	-5.3 to -4.0	-1.1	-1.8 to -0.5	<0.0001
Fasting plasma glucose (mmol/l)	-0.34	-0.45 to -0.24	0.01	-0.10 to 0.11	<0.0001
2-h plasma glucose (mmol/l)	-1.08	-1.41 to -0.75	-0.43	-0.76 to -0.10	0.006
Fasting serum insulin (mU/l)	-3.0	-3.9 to -2.0	-0.7	-1.6 to 0.3	0.001
2-h serum insulin (mU/l)	-30.1	-38.4 to -21.8	-10.0	-18.4 to -1.6	0.0009
HbA _{1c} (%)	-0.07	-0.17 to 0.03	0.17	0.07 to 0.27	0.0008 ^b
HOMA-IR	-1.04	-1.35 to -0.74	-0.14	-0.45 to 0.17	<0.0001
PAI-1 (U/ml)	-9.4	-12.2 to -6.7	-0.3	-3.2 to 2.5	<0.0001
Fibrinogen (g/l)	-0.06	-0.16 to 0.04	0.02	-0.08 to 0.12	0.29
Dietary fat (E%)	-3.5	-4.8 to -2.3	-2.4	-3.7 to -1.2	0.21
Saturated fat (E%)	-3.0	-3.7 to -2.2	-1.6	-2.4 to -0.9	0.01
Dietary fibre (g/1000 kcal)	3.1	2.4 to 3.8	0.9	0.2 to 1.6	<0.0001
Moderate to vigorous LTPA (min/week)	40.6	14.3 to 66.8	6.0	-20.8 to 32.7	0.07 ^c

Data were analysed using a general linear mixed model

^a*p* value for change with

group×time interaction

^b*p* value for Wilcoxon's signed-rank test: *p*=0.0005 in the intervention group,

p=0.0343 in the control group

^c*p* value for the Wilcoxon's signed-rank test: *p*=0.0005 in the intervention group, *p*=0.0918 in the control group

Fig. 1 Changes in PAI-1 during the first year according to the Success Score. The Score describes the number of the predefined lifestyle goals achieved. The linear trend in the success score and PAI-1 changes was significant, $p=0.008$. The description of the score is given in the [Subjects and Methods](#) section. The numbers below the bars indicate the number of subjects in each category

PAI-1 activity decreased significantly after the 1-year intervention (31%), but no change was observed in the control group. Fibrinogen did not change during the 1-year period in either group. PAI-1 changes were associated with the success score at 1-year follow-up: the higher the score the larger the decrease in PAI-1 ($p=0.008$) (Fig. 1). During the first follow-up year, PAI-1 decreased more in subjects who did not develop diabetes ($n=251$) than in those ($n=70$) who did during the DPS follow-up of 3.2 years (6.2 ± 17.3 U/ml vs 0.5 ± 22.1 U/ml, $p=0.02$).

The most important factor explaining the change in PAI-1 was the change in weight (R^2 10.7%, $p<0.0001$). Other explanatory factors were the following: insulin resistance (HOMA-IR) (R^2 6.3%, $p<0.0001$), fat intake (R^2 5.6%, $p<0.0001$), fibre intake (R^2 4.4%, $p=0.0002$), saturated fat intake (R^2 3.7%, $p=0.0005$), 2-h glucose (R^2 2.7%, $p=0.003$) and LTPA (R^2 2.1%, $p=0.01$). In the final model, including weight, fat intake, and moderate to vigorous LTPA as covariates, the change in PAI-1 in the intervention group was reduced from the unadjusted value of -9.4 U/ml (95% CI -12.2 to -6.7) to -5.2 U/ml (95% CI -8.1 to -2.3) (Table 3).

In the Turku subgroup, levels of PAI-1 at the 1- and 3-year follow-ups compared with the baseline values remained the same in the intervention group (-35% vs -37%) while the decrease in the control group was greater at the 3-year follow-up than at 1-year (-23% vs -9%). PAI-1 changes with group $\times$ time interaction were still significant ($p=0.009$). The changes in fibrinogen at 1 and 3 years were

-1% vs -10% in the intervention group and -1% vs -5% in the control group ($p=0.38$).

Discussion

The Finnish DPS showed that intensive dietary and exercise intervention had long-term beneficial effects on fibrinolysis as measured by the plasma PAI-1 level. The decrease in PAI-1 was associated with weight reduction. During the first year, the subjects in the intervention group lost an average of 4.7 kg and their PAI-1 activity decreased by 31%. The decrease in PAI-1 persisted in our intervention group, and so did the decrease of weight, up to the 3-year follow-up. To our knowledge, no other report has covered such a long follow-up period. Our 1-year results are in accordance with those previously obtained in a Swedish study [20]. In connection with the weight decline, our subjects' insulin sensitivity improved, which may partly explain the reduction in PAI-1 [30]. Surprisingly, there is one lifestyle intervention study in which marked weight loss and a decrease in insulin resistance were not accompanied by any decrease in PAI-1 [21]. The decline of PAI-1 has been shown to be more closely related to changes in adipose tissue than to changes in insulin levels [31]. Several studies have shown decreased PAI-1 levels after weight loss [17, 18, 30–32], and the decrease seems to depend on the magnitude of the weight loss [17]. Furthermore, the PAI-1 level has been shown to increase when weight is regained [31].

Besides weight loss, changes in energy intake from fat, saturated fat and dietary fibre were associated with the PAI-1 decrease. Fibre intake, however, had no independent explanatory power, as has been shown previously [33, 34]. All changes in the dietary components were connected with changes in weight. It seems probable that neither modification of dietary fat composition alone nor a reduction of dietary fat intake will alter the PAI-1 levels without the occurrence of a significant weight loss [35, 36].

In our study, exercise training had a smaller impact on the PAI-1 levels than the decrease in weight. The participants were at first advised to change their diet, and the exercise programmes did not start until after the first 6 months of the DPS. The intervention group was advised and supervised to carry out individually tailored progressive exercise programmes including resistance training throughout the study period. Consequently, the changes in

Table 3 One-year changes in PAI-1 activity (U/ml) in the intervention and control groups with different adjustments

Variables adjusted for	Intervention group		Control group		p^a
	Change	95% CI	Change	95% CI	
None	-9.44	-12.23 to -6.66	-0.34	-3.17 to 2.49	<0.0001
Weight (kg)	-6.54	-9.31 to -3.77	+0.37	-2.38 to 3.99	0.0005
Fibre (g/kcal)	-7.08	-10.05 to -4.10	+0.39	-2.45 to 3.23	0.0003
Dietary fat (E%)	-7.53	-10.37 to -4.69	+1.01	-1.82 to 3.85	<0.0001
Saturated fat (E%)	-7.65	-10.60 to -4.69	+0.68	-2.20 to 3.55	<0.0001
Exercise ^b	-9.21	-12.08 to -6.33	-0.62	-3.52 to 2.29	<0.0001
Weight+fat ^c +exercise	-5.17	-8.06 to -2.28	+1.10	-1.73 to 3.94	0.0009

^a p value denotes the significance for change with group $\times$ time interaction

^bExercise denotes moderate to vigorous LTPA

^cFat denotes dietary fat (E%)

fibrinogen were greater after the third year than after the first year. The effects of exercise may be partly mediated by visceral fat loss [37], which can determine PAI-1 levels [31, 38, 39]. The type and intensity of exercise may be important because in some studies exercise has caused no additional effect after dieting [40]. High-intensity exercise may be needed to induce significant changes in PAI-1 levels [41, 42]. We have previously shown that the increase in moderate to vigorous physical activity decreased the risk of type 2 diabetes in subjects with IGT [28]. However, all life-style changes are important, and in our study they all explained the PAI-1 decrease; the better the intervention goals were achieved, the greater was the decrease in PAI-1.

The results of the intervention persisted for 3 years, but the difference between the intervention and control groups diminished, because PAI-1 decreased in the control group, too. One explanation may be that subjects developing diabetes during the first and second years did not take part in the 3-year follow-up and all but two of these belonged to the control group. Since those developing diabetes had no decrease in PAI-1 at year 1, if tested, they would probably also have no decline at 3 years. Thus, their absence from the 3-year data results in a greater decrease in PAI-1 at 3 years compared with 1 year among subjects in the control group.

The changes in fibrinogen levels were small during the first year, which is in line with many dietary and exercise intervention studies on subjects with or without glucose intolerance [17, 18, 32, 34–36, 40, 43]. The reason may be that the change in weight was relatively small. One study that found an average weight loss of 13.6 kg showed a marked decline in fibrinogen [18]. In one lifestyle intervention study the beneficial effect of intervention on fibrinogen was actually the result of the increase in fibrinogen in the control group, while the decrease in the intervention group was not significant [20]. Diabetic patients with higher physical activity and higher aerobic power had lower fibrinogen concentrations in plasma [44], but in exercise intervention studies comprising normal or diabetic subjects the changes in fibrinogen have been conflicting [42, 45–47]. In the DPP study, after the first year the change in fibrinogen was –2% in the lifestyle group [48], which is slightly more than in our study. At the 3-year follow-up we found a decrease of 10% in the fibrinogen level in the intervention group. This may be the result of the moderate to vigorous exercise, which was reported to increase markedly [28]. Thus, intensive exercise may be necessary to achieve a significant decrease in fibrinogen [42].

In conclusion, intensive lifestyle intervention, which reduced the risk of type 2 diabetes in IGT subjects, was accompanied by a marked decrease in PAI-1 levels. The decrease of PAI-1 was mainly explained by weight reduction. Thus, these favourable changes in the fibrinolytic system and metabolic factors in IGT subjects can improve the cardiovascular profile in these high-risk individuals.

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