# Lifestyle Changes May Reverse Development of the Insulin Resistance Syndrome

## The Oslo Diet and Exercise Study: a randomized trial

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**OBJECTIVE** — To compare and assess the single and joint effect of diet and exercise intervention for 1 year on insulin resistance and the development leading toward the insulin resistance syndrome.

**RESEARCH DESIGN AND METHODS** — An unmasked, randomized 2 × 2 factorial intervention trial was applied with a duration of 1 year for each participant. The trial comprised 219 men and women with diastolic blood pressure of 86–99 mmHg, HDL cholesterol <1.20 mmol/l, triglycerides >1.4 mmol/l, total cholesterol of 5.20–7.74 mmol/l, and BMI >24 kg/m$^2$. Participants were randomly allocated to diet group ($n$ = 55), diet and exercise group ($n$ = 67), exercise group ($n$ = 54), and control group ($n$ = 43). The diet included increased intake of fish and reduced total fat intake. The exercise program entailed supervised endurance exercise three times a week. Baseline cross-sectional changes and 1-year changes in insulin resistance, fasting serum levels of insulin, C-peptide, proinsulin, glucose, and lipids as well as weight, mean blood pressure, and plasminogen activator inhibitor 1 (PAI-1) values were recorded.

**RESULTS** — The cross-sectional results at baseline showed significant correlations between the calculated insulin resistance and BMI ($r$ = 0.54) and correlations between the mean blood pressure (mBP) ($r$ = 0.26) and PAI-1 ($r$ = 0.40). The 1-year diet intervention gave a significant decrease in the calculated insulin resistance from 4.6 to 4.2 and a positive correlation between the changes in insulin resistance and changes in BMI ($r$ = 0.40). The diet and exercise intervention also led to significantly decreased insulin resistance (from 5.0 to 4.0). The exercise intervention did not significantly change insulin resistance.

**CONCLUSIONS** — The cross-sectional and 1-year intervention results supported each other and underscored the important connection between increased BMI and the development leading toward the insulin resistance syndrome.

Several studies have indicated that hyperinsulinemia caused by insulin resistance may be a risk factor for cardiovascular disease in men (1–3) and probably operates through its common association with other important risk factors constituting a metabolic cardiovascular risk syndrome. In 1988, Reaven (4) called this association of cardiovascular risk factors syndrome X and included in the syndrome the following: *1*) resistance to insulin-stimulated glucose uptake, 2) glucose intolerance, 3) hyperinsulinemia, 4) increased very-low-density lipoprotein triglyceride, 5) decreased HDL cholesterol, and *6*) hypertension.

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dBP, diastolic blood pressure; MANOVA, multivariate analysis of variance; mBP, the mean blood pressure; ODES, Oslo Diet and Exercise Study; PAI-1, plasminogen activator inhibitor 1; PLSD, partial least-square difference; mBP, mean blood pressure; sBP, systolic blood pressure.

A more appropriate name may be the atherothrombogenic syndrome, as suggested by Hjermann (5), or the insulin resistance syndrome, as used by Bierman (6). Haffner et al. (7) showed that fasting serum levels of insulin were related to the incidence of hypertension, decreased levels of HDL cholesterol, increased levels of triglycerides, and the development of type II diabetes. Lately, elevated levels of the plasminogen activator inhibitor 1 (PAI-1) were included in the syndrome (8). The Western lifestyle, with its high prevalence of obesity and poor physical exercise capacity, is thought to be central in the development of this syndrome, and increased physical exercise and/or diet restrictions would probably reverse the development of the syndrome.

We studied whether lifestyle changes could reverse the development leading toward hyperinsulinemia and its accompanying metabolic disturbances. For this purpose we used data from the Oslo Diet and Exercise Study (ODES) because the participants showed many of the characteristics of the insulin resistance syndrome. In a recent paper (11), we reported in detail how various effects of physical training and dietary intervention improved carbohydrate metabolism and associated coronary risk variables. In the present paper, we report how the effects of the different intervention strategies influenced insulin resistance in the context of the insulin resistance syndrome.

## RESEARCH DESIGN AND METHODS

— The experimental design, recruitment of participants, laboratory procedures, and intervention program have been described earlier (9,10). In short, the study was a 2 × 2 randomized primary preventive trial with duration of 1 year, the two interventions being physical exercise and dietary change. Thus the participants were randomized to the following four groups: diet group ($n$ = 55), diet and excercise group ($n$ = 67), exercise group ($n$ = 54), and control group ($n$ = 43).

The participants were recruited from a continuously ongoing screening of 40-year-

Table 1—*Baseline values of variables in each intervention group*

| Variable | Intervention group | | | |
|---|---|---|---|---|
| | Diet | Diet and exercise | Exercise | Control |
| *n* | 52 | 65 | 49 | 43 |
| Insulin resistance | 4.60 ± 2.10 | 5.03 ± 3.48 | 5.05 ± 3.12 | 4.89 ± 4.64 |
| β-cell function (%) | 179 ± 71 | 203 ± 105 | 201 ± 90 | 207 ± 107 |
| Fasting insulin (pmol/l) | 130 ± 52 | 143 ± 82 | 145 ± 77 | 142 ± 108 |
| Fasting C-peptide (pmol/l) | 1,073 ± 473 | 1,187 ± 554 | 1,222 ± 551 | 1,111 ± 686 |
| Fasting proinsulin (pmol/l) | 14 ± 11 | 14 ± 15 | 15 ± 14 | 15 ± 22 |
| Fasting glucose (mmol/l) | 5.65 ± 0.81 | 5.60 ± 0.96 | 5.65 ± 0.56 | 5.41 ± 0.52 |
| Post–oral glucose glucose (mmol/l) | 8.45 ± 2.52 | 8.53 ± 2.31 | 7.88 ± 2.03 | 7.85 ± 2.20 |
| BMI (kg/m²) | 29.7 ± 4.2 | 28.6 ± 3.4 | 28.6 ± 3.1 | 28.3 ± 3.1 |
| mBP (mmHg) | 100 ± 10 | 99 ± 9 | 101 ± 9 | 98 ± 8 |
| Fasting triglycerides (mmol/l) | 2.39 ± 1.35 | 2.37 ± 1.60 | 2.30 ± 1.10 | 2.29 ± 0.84 |
| Fasting HDL cholesterol (mmol/l) | 0.93 ± 0.22 | 0.99 ± 0.21 | 1.02 ± 0.21 | 1.05 ± 0.17 |
| PAI-1 (U/ml) | 22 ± 17 | 21 ± 16 | 19 ± 11 | 18 ± 14 |

Data are means ± SD.

old men and women in Oslo since 1981, recording important cardiovascular risk factors in those who every year pass into their 40s. From this database we selected men and women relatively inactive (exercising at most once per week and characterized by a maximal oxygen uptake [$Vo_{2max}$] of 35.4 ± 5.9 ml · $kg^{-1}$ · $min^{-1}$, mean ± SD at the start of intervention) as measured by a questionnaire, with BMI of >24 kg/m², diastolic blood pressure of 86–99 mmHg, total cholesterol of 5.20–7.74 mmol/l, HDL cholesterol of <1.20 mmol/l, and fasting triglycerides >1.4 mmol/l at the primary screening. All criteria had to be fulfilled for each participant. Furthermore, the participants had no overt cardiovascular disease or diabetes and used no drugs that might have interfered with test results. A total of 219 men and women fulfilled all the inclusion criteria and were randomized to one of the four groups defined above.

## Methods

**Glucose tolerance test.** Insulin, C-peptide, proinsulin, and glucose were measured both in serum drawn before and 60 min after a standard oral glucose load of 75 g at baseline and again after 1 year. All measurements from each subject were determined in one assay series.

**Measurements and analyses.** Analyses were performed batchwise from frozen samples after the closure of the trial. Insulin was assayed by a radioimmunoassay using an antibody with no cross-reaction against proinsulin or des 31,32 split proinsulin (12). C-peptide was assayed by a radioimmunoassay with 5% cross-reaction against proinsulin (Diagnostic System Laboratories, Webster, TX). Proinsulin was measured by an immunometric assay using monoclonal antibodies against the insulin and C-peptide parts (12). Other components were determined with standard methods (9,10).

**Calculation of insulin resistance and β-cell function.** Insulin resistance and relative β-cell function were calculated from the fasting serum levels of glucose and insulin according to the homeostasis model developed by Matthews et al. (13). Insulin resistance and relative β-cell function for the individual subject were determined according to the following formulas: resistance = (insulin/7.2)/(22.5/glucose); relative β-cell function (%) = (20 × insulin/7.2)/(glucose − 3.5). The insulin values were divided by 7.2 to obtain milliunits per liter from picomoles per liter.

**Statistical analysis.** A global statistical test for interaction between diet and exercise and for overall differences between groups for all four outcomes was done by multivariate analysis of variance (MANOVA) (10). Six contrasts were specified to be of interest: 1) diet and exercise group versus diet group, 2) diet and exercise group versus exercise group, 3) diet and exercise group versus control group, 4) diet group versus control group, 5) exercise group versus control group, and 6) diet group versus exercise group. The comparison for each outcome was performed by independent *t* test according to Fisher's partial least-square difference (PLSD) multiple comparison rule with 5% overall significance level. Other statistical tests were performed by the SigmaStat (Jandel Scientific, Erkrath, Germany) statistical program. The degree of explanation found by stepwise regression analysis and second-order polynomial regression was adjusted to take into account the number of independent variables, which reflected the degrees of freedom. The level of significance used was $P < 0.05$.

**RESULTS** — The calculated relative insulin resistance varied 30-fold among the subjects, as can be seen from the large

Table 2—*The response (year 1–year 0) after 1-year intervention in the variables of Table 1*

| Variable | Intervention group | | | |
|---|---|---|---|---|
| | Diet | Diet and exercise | Exercise | Control |
| Insulin resistance | −0.4 ± 0.2* | −1.0 ± 0.2* | −0.3 ± 0.4 | 0.2 ± 0.2 |
| β-cell function (%) | 6.8 ± 6.8 | −14.1 ± 8.4 | −5.5 ± 11.6 | 3.5 ± 10.9 |
| Fasting insulin (pmol/l) | −7 ± 4* | −20 ± 5*† | −7 ± 9 | 4 ± 6 |
| Fasting C-peptide (pmol/l) | −163 ± 49*‡ | −355 ± 33*† | −291 ± 49*† | −92 ± 53 |
| Fasting proinsulin (pmol/l) | −2.2 ± 1.1*† | −3.7 ± 0.7*† | −2.7 ± 0.8*† | 1.6 ± 1.2 |
| Fasting glucose (mmol/l) | −0.2 ± 0.1*† | −0.3 ± 0.1*† | −0.1 ± 0.1 | 0.0 ± 0.1 |
| Post–oral glucose glucose (mmol/l) | −0.3 ± 0.2 | −0.6 ± 0.2* | −0.5 ± 0.3 | −0.2 ± 0.3 |
| BMI (kg/m²) | −1.3 ± 0.2* | −3.7 ± 0.7*§ | −0.3 ± 0.2 | 0.4 ± 0.1* |
| mBP (mmHg) | −5.2 ± 1.1*† | −6.1 ± 0.9*† | −3.2 ± 1.0*‡ | −1.5 ± 1.5 |
| Fasting triglycerides (mmol/l) | −0.3 ± 0.2†‡ | −0.7 ± 0.2*† | −0.3 ± 0.1*†‡ | −0.1 ± 0.3 |
| Fasting HDL cholesterol (mmol/l) | 0.06 ± 0.04*‡ | 0.10 ± 0.02*† | 0.02 ± 0.02‡ | −0.05 ± 0.03 |
| PAI-1 (U/ml) | 0.9 ± 3.8 | 3.4 ± 3.3 | 5.3 ± 3.9 | 2.4 ± 3.3 |

Wilcoxon's signed-rank test and Mann-Whitney sum test were used throughout, even where parametric tests could have been employed, to facilitate comparison of test results. In all applicable cases the parametric and nonparametric tests gave identical statistical significance ($P < 0.05$). See also Fig. 1. Data are means ± SD. *$P < 0.05$, Wilcoxon's signed-rank test; †$P < 0.05$, Fisher's PLSD test, intervention group versus control; ‡$P < 0.05$, Fisher's PLSD test, diet and exercise versus diet or exercise; §$P < 0.05$, Mann-Whitney U rank sum test, diet and exercise versus exercise or control.

**Table 3—P *values for the Wilcoxon's signed-rank tests of Table 2***

| Variable | Intervention group | | | |
|---|---|---|---|---|
| | Diet | Diet and exercise | Exercise | Control |
| Insulin resistance | −0.4 (0.01) | −1.0 (<0.0001) | −0.3 (0.18) | 0.2 (0.45) |
| β-cell function (%) | 6.8 (0.40) | −14.1 (0.13) | −5.5 (0.69) | 3.5 (0.40) |
| Fasting insulin (pmol/l) | −7 (0.049) | −20 (<0.0001) | −7 (0.17) | 4 (0.53) |
| Fasting C-peptide (pmol/l) | −163 (<0.0001) | −355 (<0.0001) | −291 (<0.0001) | −92 (0.08) |
| Fasting proinsulin (pmol/l) | −2.2 (0.006) | −3.7 (<0.0001) | −2.7 (<0.0001) | 1.6 (0.73) |
| Fasting glucose (mmol/l) | −0.2 (0.002) | −0.3 (<0.0001) | −0.1 (0.20) | 0.0 (0.93) |
| Post–oral glucose glucose (mmol/l) | −0.3 (0.28) | −0.6 (0.012) | −0.5 (0.14) | −0.2 (0.74) |
| BMI (kg/m²) | −1.3 (<0.0001) | −3.7 (<0.0001) | −0.3 (0.38) | 0.4 (0.006) |
| mBP (mmHg) | −5.2 (<0.0001) | −6.1 (<0.0001) | −3.2 (0.005) | −1.5 (0.36) |
| Fasting triglycerides (mmol/l) | −0.3 (0.11) | −0.7 (<0.0001) | −0.3 (0.046) | −0.1 (0.78) |
| Fasting HDL cholesterol (mmol/l) | 0.06 (0.013) | 0.10 (<0.0001) | 0.02 (0.37) | −0.05 (0.10) |
| PAI-1 (U/ml) | 0.9 (0.72) | 3.4 (0.55) | 5.3 (0.46) | 2.4 (0.34) |

Data are means (*P* value).

standard deviations (Table 1). Despite the large variation among the individuals, the diet intervention lowered the mean insulin resistance within the group during 1 year from 4.6 to 4.2, while the diet and exercise intervention lowered it from 5.0 to 4.0. Insignificant changes were observed after the exercise intervention and in the control group (Tables 2 and 3). No significant changes were observed in the calculated relative β-cell function after intervention.

Only small changes were observed in the fasting insulin levels during the intervention, although significant reductions were observed in the diet group and diet and exercise group (Table 2 and 3). The insulin increment after oral glucose load (1-h basal) decreased within the diet and exercise group from 640 ± 60 (mean ± SE) to 480 ± 50 pmol/l, while no significant changes were observed in the other groups (not shown).

The C-peptide levels were significantly reduced after 1 year within all three intervention groups (Tables 2 and 3). In the diet and exercise group and the exercise group, the decrease was also significant when compared with the control group. The change in the diet and exercise group was significantly larger than in the diet group ($P = 0.003$).

The mean fasting serum levels of proinsulin was significantly reduced after 1 year in all three intervention groups both within the groups and relative to the control group (Tables 2 and 3).

The mean fasting serum levels of glucose were reduced −0.22 mmol/l in the diet group and −0.28 mmol/l in the diet and exercise group after 1 year of intervention (Tables 2 and 3). These changes were significant both within the groups and when compared with the control group. Because exercise alone did not significantly reduce the fasting serum levels of glucose, the diet factor was the more effective.

The diet and exercise intervention led to a significant improvement in the serum levels of glucose 1 h after the glucose load when compared with the levels before intervention (Tables 2 and 3). No significant changes were observed in the other groups.

The mean BMI for the subjects was well above the inclusion criterion of >24 kg/m² (Table 1). Within the diet group and diet and exercise group, 1 year of intervention significantly reduced the mean BMI, −1.3 vs. −3.7 kg/m², although few regained normal BMI (Tables 2 and 3). The diet and exercise group lost significantly more weight than the control group ($P < 0.0001$) and exercise group ($P = 0.002$), showing the efficacy of the combined intervention on BMI. Mean BMI increased 0.4 kg/m² within the control group during the intervention period.

Diastolic blood pressure (dBP) and systolic blood pressure (sBP) were measured at baseline and after 1 year of intervention, and mean blood pressure (mBP) was calculated. The changes in these variables correlated closely (dBP vs. sBP, $r = 0.64$; dBP vs. mBP, $r = 0.81$; sBP vs. mBP, $r = 0.69$). Because the data from the mBP measurements correlated best to the other variables (Table 4), these were presented, although essentially the same results were obtained with the two other blood pressure vari-



**Table 4—*Pearson product-moment correlation matrix between variables known to associate in the insulin resistance syndrome, and BMI and PAI-1***

| Variable | β-cell function | Insulin | C-peptide | Proinsulin | Glucose | BMI | mBP | Triglycerides | HDL cholesterol | PAI-1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Insulin resistance | 0.63 | 0.97 | 0.78 | 0.83 | 0.45 | 0.54 | 0.26 | 0.13 | −0.11 | 0.40 |
| β-cell function | — | 0.77 | 0.49 | 0.49 | −0.29 | 0.37 | 0.08 | 0.17 | −0.13 | 0.31 |
| Insulin | — | — | 0.76 | 0.78 | 0.26 | 0.53 | 0.22 | 0.15 | −0.14 | 0.41 |
| C-peptide | — | — | — | 0.67 | 0.39 | 0.52 | 0.32 | 0.29 | −0.22 | 0.43 |
| Proinsulin | — | — | — | — | 0.37 | 0.46 | 0.25 | 0.18 | −0.17 | 0.38 |
| Glucose | — | — | — | — | — | 0.27 | 0.22 | 0.00 | −0.02 | 0.16 |
| BMI | — | — | — | — | — | — | 0.23 | 0.02 | −0.05 | 0.26 |
| mBP | — | — | — | — | — | — | — | 0.12 | −0.05 | 0.23 |
| Triglycerides | — | — | — | — | — | — | — | — | 0.43 | 0.31 |
| HDL cholesterol | — | — | — | — | — | — | — | — | — | −0.23 |

Cross-sectional analysis before intervention: correlations above $r = 0.13$ ($n = 209$) are statistically significant ($P < 0.05$).

**Table 5—*Effect of diet intervention***

| Variable | β-cell function | Insulin | C-peptide | Proinsulin | Glucose | BMI | mBP | Triglycerides | HDL cholesterol | PAI-1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Insulin resistance | 0.32 | 0.94 | 0.62 | 0.65 | 0.48 | 0.40 | 0.26 | 0.27 | −0.04 | −0.03 |
| β-cell function | — | 0.58 | 0.24 | 0.11 | −0.46 | 0.12 | 0.08 | 0.08 | −0.01 | 0.00 |
| Insulin | — | — | 0.59 | 0.54 | 0.25 | 0.41 | 0.20 | 0.26 | −0.08 | 0.01 |
| C-peptide | — | — | — | 0.39 | 0.35 | 0.38 | 0.31 | 0.32 | −0.11 | −0.04 |
| Proinsulin | — | — | — | — | 0.37 | 0.21 | 0.09 | 0.26 | −0.026 | 0.07 |
| Glucose | — | — | — | — | — | 0.31 | 0.33 | 0.01 | −0.11 | 0.01 |
| BMI | — | — | — | — | — | — | 0.39 | 0.21 | −0.08 | 0.25 |
| mBP | — | — | — | — | — | — | — | 0.31 | −0.16 | 0.32 |
| Triglycerides | — | — | — | — | — | — | — | — | −0.13 | 0.40 |
| HDL cholesterol | — | — | — | — | — | — | — | — | — | −0.22 |

Pearson product correlation matrix between changes in variables that associate in the insulin-resistance syndrome, and BMI and PAI-1. Correlations above $r = 0.27$ ($n = 52$) are statistically significant ($P < 0.05$).

ables. The diet intervention schedules decreased the mBP −5.2 mmHg, the exercise intervention −3.2 mmHg, and the diet and exercise intervention −6.1 mmHg within the groups (Tables 2 and 3). The exercise intervention changed the mBP less than the exercise and diet intervention ($P < 0.05$), while no difference was observed between diet intervention alone and diet and exercise intervention.

PAI-1 values showed a wide variation between individuals (Table 1) and did not show any significant changes after 1 year in any of the intervention groups (Tables 2 and 3). Several primary and secondary hemostatic variables were assayed in the study, but the baseline values of PAI-1 correlated best with the variables of the insulin resistance syndrome (Table 4). Pearson product-moment correlation between insulin resistance and globulin clot lysis time gave $r = 0.31$, and insulin resistance versus tissue plasminogen activator gave $r = 0.19$.

The calculated baseline insulin resistance showed positive cross-sectional correlations with BMI, mBP, and PAI-1 (Table 4). The β-cell function correlated with BMI and triglyceride values. Stepwise regression analysis entering baseline BMI, mBP, triglyceride, HDL, and PAI-1 as candidate independent variables versus insulin resistance, relative β-cell function, and other carbohydrate-related variables as dependent variables showed that the BMI and PAI-1 values could explain 35% of the calculated insulin resistance. Linear regression analysis showed that 29% of the calculated insulin resistance could be explained from the BMI values. The *F* statistic (which gauges the contribution of the regression equation to predict the dependent variable) had a value of 81 in the linear analysis versus 51 in the step-2 analysis, indicating that the unexplained variability was smaller than what was expected from random sampling variability in the dependent variable about its mean using the linear regression mode. A highly significant correlation ($r = 0.57$) resulted from a second-order polynomial regression entering BMI as independent and insulin resistance as dependent variable. Although 32% of the insulin resistance could be explained from BMI using this second-order polynomial regression analysis, the value of the *F* statistic was only 49, indicating that linear regression between BMI and insulin resistance was probably the more reliable. These regression results showed that BMI was a strong predictor for insulin resistance and, furthermore, that PAI-1 in many individuals strengthened this prediction.

A step-4 regression showed that 44% of the fasting serum levels of C-peptide could be explained by the BMI, PAI-1, mBP, and triglyceride values ($r = 0.66$). Although the *F* statistic was only 39, the analysis showed how several non carbohydrate variables contributed to this aspect of the β-cell function

The effects of diet intervention on the changes in the variables known to associate in the insulin resistance syndrome were tested for significant correlation (Table 5). A significant correlation ($r = 0.40$) was obtained between the change in relative insulin resistance and BMI. The corresponding linear regression entering the change in BMI as independent and insulin resistance as dependent variable is illustrated in Fig. 1.

The effects of the diet and exercise intervention on the changes in several relevant variables were tested for correlation as above (Table 6). No significant correlations were found between the changes in the insulin resistance and the non−carbohydrate-related variables.

The effects of the exercise intervention on the changes in several relevant factors were tested for correlation as above (Table 7). A significant correlation ($r = 0.47$) was found between the changes in the relative insulin resistance and the changes in triglyceride levels. The corresponding linear regression entering the changes in

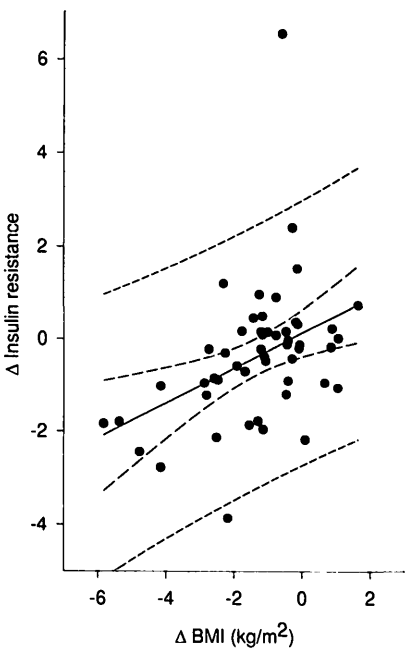


**Figure 1**—*Linear regression: The diet-intervention–induced changes in BMI values were entered as the independent variable and changes in the calculated insulin resistance as the dependent variable. Also, 95% confidence limits within the prediction interval are shown. The regression equation is* $Y = 0.39X + 0.12$, $r = 0.40$, $n = 51$.

**Table 6—*Effect of diet and exercise intervention***

| Variable | β-cell function | Insulin | C-peptide | Proinsulin | Glucose | BMI | mBP | Triglycerides | HDL cholesterol | PAI-1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Insulin resistance | 0.44 | 0.88 | 0.34 | 0.60 | 0.44 | 0.14 | −0.08 | −0.04 | −0.01 | 0.17 |
| β-cell function | — | 0.74 | 0.17 | 0.17 | −0.53 | 0.04 | 0.04 | 0.11 | 0.04 | −0.09 |
| Insulin | — | — | 0.34 | 0.42 | −0.01 | 0.15 | 0.07 | 0.08 | 0.07 | 0.19 |
| C-peptide | — | — | — | 0.21 | 0.18 | 0.26 | 0.23 | 0.37 | −0.24 | −0.18 |
| Proinsulin | — | — | — | — | 0.37 | 0.21 | 0.06 | 0.01 | −0.09 | −0.13 |
| Glucose | — | — | — | — | — | 0.14 | −0.18 | −0.19 | 0.02 | 0.08 |
| BMI | — | — | — | — | — | — | 0.40 | 0.00 | −0.11 | −0.04 |
| mBP | — | — | — | — | — | — | — | 0.22 | −0.17 | 0.20 |
| Triglycerides | — | — | — | — | — | — | — | — | −0.47 | 0.29 |
| HDL cholesterol | — | — | — | — | — | — | — | — | — | 0.07 |

Pearson product-moment correlation matrix between changes in variables that associate in the insulin-resistance syndrome, and BMI and PAI-1. Correlations above $r = 0.24$ ($n = 65$) are statistically significant ($P < 0.05$).

triglycerides as independent and insulin resistance as dependent variable is illustrated in Fig. 2.

**CONCLUSIONS** — The development of the insulin resistance or atherothrombogenic syndrome is a gradual process that spans many years. Many participants in the ODES were probably on the verge of developing the syndrome, as their relative insulin resistance, glucose tolerance, and other factors showed. Accordingly, it is of significance that all three intervention schedules were able to reverse the process leading toward the syndrome, as judged by the improvements in relevant variables. In the control group, the small deterioration observed in the values of several assayed variables fitted nicely with a gradual development toward the insulin resistance syndrome in sedentary middle-aged people.

A useful characterization of the process leading toward the insulin resistance syndrome was dependent on good analytical methods for the variables of the syndrome. Ideally, the resistance to insulin-stimulated glucose uptake should have been determined by the euglycemic-hyperinsulinemic glucose clamp technique (14). Because this was not feasible in a large study like the present, the relative insulin resistance and the relative β-cell function were calculated from the homeostasis model devised by Matthews et al. (13). Values obtained for the relative insulin resistance and the relative β-cell function in the present study were within the range found by Matthews et al. (13). Regression studies entering BMI as the independent and insulin resistance as the dependent variable gave highly significant correlations and showed that one-third of the insulin resistance at baseline could be explained from the BMI, showing the relationship between degree of obesity and in vivo insulin action in humans (17).

In contrast to the effect of the intervention schedules on the insulin resistance, only small changes in the relative β-cell function were observed, whether assessed by Matthews's model (13) or by the insulin response to glucose. Thus, the improvement in glucose tolerance was not caused by increased insulin secretion, but rather by improved efficacy of the insulin secreted in accordance with the decreased insulin resistance measured and the decreased fasting levels of C-peptide.

It is of interest that the fasting proinsulin levels correlated significantly with lipid and blood pressure levels and were stronger than the fasting insulin levels. This confirms previously reported findings in nondiabetic (15) and type II diabetic subjects (16) and extends these findings to a group of subjects selected as having an "insulin resistance" metabolic profile.

Taken together, the results suggested that diet and exercise intervention was the

**Table 7—*Effect of exercise intervention***

| Variable | β-cell function | Insulin | C-peptide | Proinsulin | Glucose | BMI | mBP | Triglycerides | HDL cholesterol | PAI-1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Insulin resistance | 0.74 | 0.99 | 0.66 | 0.72 | 0.23 | 0.13 | −0.02 | 0.47 | −0.12 | 0.12 |
| β-cell function | — | 0.82 | 0.36 | 0.51 | −0.38 | −0.01 | −0.01 | 0.31 | −0.12 | 0.10 |
| Insulin | — | — | 0.63 | 0.71 | 0.11 | 0.11 | −0.02 | 0.45 | −0.11 | 0.10 |
| C-peptide | — | — | — | 0.54 | 0.30 | 0.31 | 0.02 | 0.44 | −0.18 | 0.16 |
| Proinsulin | — | — | — | — | 0.19 | 0.04 | −0.10 | 0.43 | −0.12 | 0.07 |
| Glucose | — | — | — | — | — | 0.28 | 0.15 | 0.11 | −0.05 | 0.11 |
| BMI | — | — | — | — | — | — | 0.18 | 0.25 | −0.35 | 0.06 |
| mBP | — | — | — | — | — | — | — | 0.14 | −0.11 | −0.04 |
| Triglycerides | — | — | — | — | — | — | — | — | −0.54 | 0.04 |
| HDL cholesterol | — | — | — | — | — | — | — | — | — | −0.04 |

Pearson product-moment correlation matrix between changes in variables that associate in the insulin-resistance syndrome and BMI and PAI-1. Correlations above $r = 0.28$ ($n = 49$) are statistically significant ($P < 0.05$).

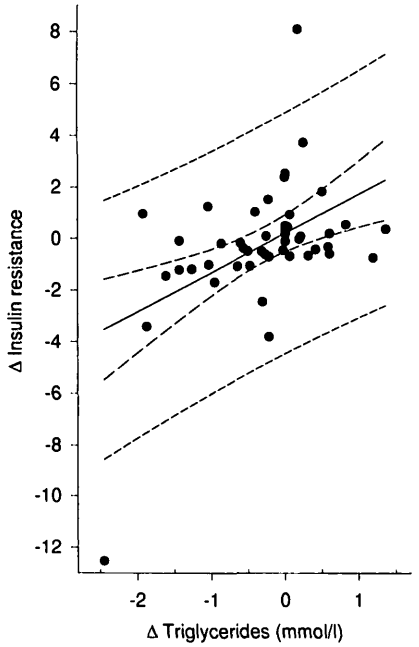


**Figure 2**—*Linear regression: The exercise-intervention–induced changes in the triglyceride levels were entered as the independent variable and changes in the calculated insulin resistance as the dependent variable. Also, 95% confidence limits within the prediction interval are shown. The regression equation is* $Y = 1.51X + 0.17$, $r = 0.47$, $n = 47$.

most effective in reversing the development toward the insulin resistance syndrome. Whether diet intervention was more effective than exercise or vice versa differed among the variables measured. Thus, diet intervention was the more effective on the fasting serum levels of glucose, insulin resistance, BMI, and mBP reduction, while exercise intervention was the more effective on C-peptide and triglyceride reduction. On other factors, no significant difference could be detected in the efficacy of the two schedules.

The cross-sectional and 1-year intervention results supported each other and underscored the important connection between BMI and the development leading toward the insulin resistance syndrome. The high degree of explanation for the progress of insulin resistance owing to the PAI-1 values should warrant further investigations to elucidate the mechanism(s) of this connection.

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