

Effect of Progression From Impaired Glucose Tolerance to Diabetes on Cardiovascular Risk Factors and Its Amelioration by Lifestyle and Metformin Intervention

The Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group*

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OBJECTIVE — Although subjects with diabetes have increased risk for cardiovascular disease (CVD), the evolution of this increased risk as pre-diabetic individuals progress to diabetes is not understood. This study examines the longitudinal relationship between selected CVD risk factors (blood pressure, triglycerides, HDL and LDL cholesterol, and LDL peak particle density [PPD]) and glycemia in the three treatment groups of the Diabetes Prevention Program.

RESEARCH DESIGN AND METHODS — A total of 3,234 participants with impaired glucose tolerance (IGT) were followed for a mean of 3.2 years after randomization to intensive lifestyle intervention (ILS), metformin, or placebo. Using repeated-measures models, adjusted mean levels of risk factors were estimated for an annual change in glycemic status. Tests were also conducted to assess the risk factor trends with improvement or worsening of glycemic status.

RESULTS — CVD risk factor values and changes from baseline became more unfavorable as glucose tolerance status deteriorated but improved with reversion to normal glucose tolerance (NGT), especially in the ILS intervention group (trend test $P < 0.001$ for all risk factors except for LDL PPD [$P = 0.02$] in ILS and HDL cholesterol [$P = 0.02$] in placebo). Although there were few significant differences in the transition from IGT to diabetes, there were strong relationships between risk factors and continuous measures of glycemia.

CONCLUSIONS — Progression from IGT to diabetes is associated with mild deterioration, whereas reversion to NGT is associated with improvement in risk factors. Early intervention with ILS, but less so with metformin, in participants at high risk for diabetes improves the cardiovascular risk and glucose tolerance profile simultaneously.

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Cardiovascular disease (CVD) is the major cause of morbidity and mortality in diabetes (1). Although the excess risk for CVD in diabetes has been linked to a clustering of risk factors that include blood pressure and lipoprotein abnormalities (2), little is known about the evolution of this risk as pre-diabetic individuals progress toward diabetes. An adverse pattern of CVD risk factors is already present in normoglycemic subjects who subsequently develop diabetes compared with those who do not (3), suggesting that factors other than worsening hyperglycemia are responsible for the origins of the increased cardiovascular risk in diabetes. However, no studies have prospectively evaluated the effects of deterioration of glycemia on CVD risk factors in pre-diabetic subjects in whom CVD incidence appears to be somewhat increased (4). The opportunity to examine this issue was made possible by the Diabetes Prevention Program (DPP), which studied the development of diabetes in a large population with impaired glucose tolerance (IGT) and in which intensive lifestyle (ILS) or metformin interventions were compared with placebo (5).

RESEARCH DESIGN AND METHODS

This report includes 3,234 participants in the ILS, metformin, and placebo treatment arms. Individuals were recruited from a variety of sources based on the risk for development of diabetes (5). Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines of each center's institutional review board. Eligibility was based on results of a 75-g oral glucose tolerance test (OGTT). Inclusion criteria included a fasting plasma glucose

Table 1—Baseline demographic, clinical, and laboratory characteristics by treatment group

| | Overall | Placebo | Metformin | Lifestyle | P |
|----------------------------|--------------|--------------|--------------|--------------|------|
| n | 3,234 | 1,082 | 1,073 | 1,079 | |
| Age (years) | 50.6 ± 10.7 | 50.3 ± 10.4 | 50.9 ± 10.3 | 50.6 ± 11.3 | 0.45 |
| Sex | | | | | 0.35 |
| Male | 1,043 (32.3) | 335 (31.0) | 363 (33.8) | 345 (32.0) | |
| Female | 2,191 (67.7) | 747 (69.0) | 710 (66.2) | 734 (68.0) | |
| Race/ethnicity | | | | | 0.49 |
| Caucasian | 1,768 (54.7) | 586 (54.2) | 602 (56.1) | 580 (53.8) | |
| African American | 645 (19.9) | 220 (20.3) | 221 (20.6) | 204 (18.9) | |
| Hispanic | 508 (15.7) | 168 (15.5) | 162 (15.1) | 178 (16.5) | |
| American Indian | 171 (5.3) | 59 (5.5) | 52 (4.8) | 60 (5.6) | |
| Asian American | 142 (4.4) | 49 (4.5) | 36 (3.4) | 57 (5.3) | |
| Fasting glucose (mmol/l) | 5.9 ± 0.5 | 5.9 ± 0.5 | 5.9 ± 0.5 | 5.9 ± 0.4 | 0.45 |
| 2 h glucose (mmol/l) | 9.1 ± 0.9 | 9.1 ± 1.0 | 9.2 ± 1.0 | 9.1 ± 0.9 | 0.56 |
| A1C (%) | 5.9 ± 0.50 | 5.9 ± 0.5 | 5.9 ± 0.5 | 5.9 ± 0.5 | 1.00 |
| SBP (mmHg) | 123.7 ± 14.7 | 123.5 ± 14.4 | 124.0 ± 14.9 | 123.7 ± 14.8 | 0.66 |
| DBP (mmHg) | 78.3 ± 9.3 | 78.0 ± 9.2 | 78.3 ± 9.5 | 78.6 ± 9.2 | 0.33 |
| Triglycerides (mmol/l) | 1.85 ± 1.08 | 1.91 ± 1.13 | 1.79 ± 1.02 | 1.84 ± 1.10 | 0.05 |
| Total cholesterol (mmol/l) | 5.26 ± 0.94 | 5.25 ± 0.95 | 5.25 ± 0.92 | 5.28 ± 0.95 | 0.67 |
| LDL cholesterol (mmol/l) | 3.23 ± 0.85 | 3.21 ± 0.87 | 3.23 ± 0.84 | 3.24 ± 0.85 | 0.76 |
| HDL cholesterol (mmol/l) | 1.18 ± 0.31 | 1.16 ± 0.30 | 1.19 ± 0.30 | 1.19 ± 0.32 | 0.01 |
| LDL size (RF × 1,000) | 264.4 ± 29.6 | 262.7 ± 31.1 | 265.6 ± 28.7 | 264.8 ± 29.0 | 0.06 |

Data are n (%) or means ± SD. RF, relative flotation.

value of 5.3–6.9 mmol/l (≤ 6.9 mmol/l for American Indians) and a 2-h plasma glucose of 7.8–11.1 mmol/l following the glucose load, age ≥ 25 years, and BMI ≥ 24 kg/m² (≥ 22 kg/m² for Asian Americans). Major exclusions included a recent myocardial infarction, symptoms of coronary heart disease, major illness, prior diagnosis of diabetes, or use of medications known to impair glucose tolerance.

Eligible participants were randomly assigned to one of three interventions: 850 mg metformin twice daily (MET group), placebo twice daily (placebo group), or an intensive program of lifestyle modification (ILS group). Random treatment assignments were stratified according to clinical center and double blinded for the MET and placebo groups. The goals of the ILS were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet and to engage in moderate physical activity for at least 150 min/week (5).

Diabetes was diagnosed on the basis of an annual OGTT or a semiannual fasting plasma glucose test according to American Diabetes Association (ADA) criteria (6). The diagnosis required confirmation by a second test, usually within 6 weeks. Glycated hemoglobin, systolic (SBP) and diastolic blood pressure (DBP), triglycerides, HDL cholesterol, LDL cho-

lesterol, and LDL peak particle density (PPD) (7–10) were assessed annually.

Statistical analysis

Study design and analysis were conducted according to the intention-to-treat principle. Participants were followed for an average of 3.2 years, a period 4 months longer than that reported previously when participants and staff still remained unmasked to study results (5). Comparisons among groups at baseline were made using ANOVA for quantitative variables and χ^2 test for categorical variables. Nominal P values are listed with no adjustment for multiple comparisons. Results of the OGTT were used to designate a participant's glucose tolerance status as normal glucose tolerance (NGT), IGT, or diabetes by ADA criteria (6). Mean levels of CVD risk factors at annual visits were estimated according to OGTT status and treatment group under fixed-effects models with the assumption of normally distributed errors (11). Adjustment was made for baseline risk factor levels, demographics, time from randomization, and medications influencing the risk factor level under a repeated-measures model with a first-order autoregressive (AR1) covariance structure to account for within-individual variability; in some analyses, BMI, waist circumference, or homeostasis model assessment

of insulin resistance (HOMA-IR) were included in the model.

To obtain maximal power to evaluate whether a change in OGTT status was accompanied by a change in risk factor levels, all OGTT results between any two consecutive annual visits were examined, yielding five interval patterns. These ranged from an improvement (IGT \rightarrow NGT), through lack of change in those who had achieved NGT (NGT), or remained with IGT (IGT \rightarrow IGT), to deterioration from an achieved normal to impaired (NGT \rightarrow IGT), and from normal or impaired to diabetes (NGT/IGT \rightarrow DM) status; the last two categories were combined due to small numbers in the NGT-to-diabetes category. Fixed-effects models with time-varying covariates and assumption of normally distributed errors (11) were used to estimate the adjusted mean change in risk factor levels for a change in glucose tolerance status at 1-year intervals. When available, the risk factor level at the time of diabetes diagnosis was used. Otherwise, the next available risk factor levels following diagnosis were used (47 in the placebo group, 29 in the ILS group, and 37 in the MET group) with an average time of 0.5–0.6 years from diagnosis. Excluding these intervals from the individuals did not affect the analysis, so they have been included. The analyses excluded intervals after diabetes

Table 2—Adjusted mean levels (95% CI) of cardiovascular risk factor by glucose tolerance status and treatment group at annual visits*

| | OGTT status | | | P for OGTT status | P for interaction† |
|---------------------------------|---------------------|---------------------|---------------------|-------------------|--------------------|
| | NGT | IGT | Diabetes | | |
| SBP (mmHg) | | | | | |
| ILS group | 119.0 (118.2–119.7) | 121.2 (120.4–121.9) | 123.6 (121.5–125.8) | <0.001 | 0.04 |
| MET group | 122.1 (121.3–123.0) | 123.0 (122.3–123.7) | 122.9 (121.4–124.3) | 0.17 | |
| Placebo group | 121.9 (121.0–122.8) | 123.1 (122.3–123.8) | 124.5 (123.1–125.8) | 0.003 | |
| P value for treatment | <0.001 | <0.001 | 0.29 | | |
| DBP (mmHg) | | | | | |
| ILS group | 74.0 (73.5–74.5) | 74.9 (74.4–75.4) | 77.2 (75.7–78.7) | <0.001 | <0.001 |
| MET group | 77.0 (76.4–77.6) | 76.9 (76.5–77.4) | 76.4 (75.4–77.4) | 0.55 | |
| Placebo group | 76.4 (75.8–77.0) | 76.8 (76.4–77.3) | 78.6 (77.7–79.5) | <0.001 | |
| P value for treatment | <0.001 | <0.001 | 0.004 | | |
| Triglycerides (mmol/l) | | | | | |
| ILS group | 1.46 (1.42–1.51) | 1.64 (1.59–1.68) | 1.73 (1.62–1.85) | <0.001 | 0.68 |
| MET group | 1.65 (1.60–1.70) | 1.79 (1.74–1.84) | 1.85 (1.73–1.96) | <0.001 | |
| Placebo group | 1.59 (1.53–1.65) | 1.80 (1.75–1.86) | 1.86 (1.78–1.95) | <0.001 | |
| P value for treatment | <0.001 | <0.001 | 0.20 | | |
| LDL cholesterol (mmol/l) | | | | | |
| ILS group | 3.11 (3.07–3.15) | 3.15 (3.12–3.19) | 3.12 (3.04–3.20) | 0.13 | 0.23 |
| MET group | 3.13 (3.09–3.17) | 3.15 (3.11–3.18) | 3.11 (3.04–3.18) | 0.48 | |
| Placebo group | 3.21 (3.17–3.26) | 3.19 (3.15–3.23) | 3.12 (3.06–3.18) | 0.05 | |
| P value for treatment | 0.001 | 0.21 | 0.98 | | |
| HDL cholesterol (mmol/l) | | | | | |
| ILS group | 1.22 (1.21–1.23) | 1.20 (1.19–1.21) | 1.18 (1.15–1.20) | 0.002 | 0.81 |
| MET group | 1.20 (1.19–1.22) | 1.19 (1.18–1.20) | 1.17 (1.15–1.19) | 0.02 | |
| Placebo group | 1.19 (1.18–1.20) | 1.17 (1.16–1.18) | 1.15 (1.13–1.16) | <0.001 | |
| P value for treatment | 0.001 | <0.001 | 0.08 | | |
| LDL-PPD (Rf × 1,000) | | | | | |
| ILS group | 272 (271–273) | 268 (266–269) | 263 (260–266) | <0.001 | 0.58 |
| MET group | 267 (266–269) | 265 (263–266) | 260 (257–263) | <0.001 | |
| Placebo group | 267 (265–268) | 264 (262–265) | 261 (259–263) | <0.001 | |
| P value for treatment | <0.001 | <0.001 | 0.35 | | |

*Means and CIs were obtained from fixed-effects models, with an autoregressive covariance structure to account for within-person variability and further adjustment for baseline age, sex, race/ethnicity, year of assessment, baseline CVD risk factor, and any medications that may affect the CVD risk factor. P values represent comparisons among treatment groups for each glucose tolerance category and vice versa. †The P value for interaction indicates whether the effect of the OGTT status differs by treatment group. RF, relative flotation.

diagnosis and 22 participants who developed diabetes at mid-year visits during the last 6 months of the study. The trend test was used to test the association between the changes in glucose tolerance categories and the risk factor levels using the same fixed-effects models described above but with categories coded 1 through 5. Changes in risk factor levels were also described as percent of the baseline SD to allow for comparison among the different distributions of risk factors.

RESULTS— Table 1 shows baseline characteristics, which did not differ among treatment groups except for HDL cholesterol and triglycerides. Table 2 summarizes mean risk factor levels ac-

ording to annual OGTT status by treatment group. Among the three treatment groups, HDL cholesterol, triglyceride, and LDL-PPD values differed by OGTT status ($P \leq 0.02$) as did SBP and DBP for the ILS and placebo groups. Point estimates showed more favorable risk factor levels with NGT compared with diabetes, with the IGT values being intermediate; specifically, triglycerides, LDL-PPD, and HDL cholesterol were significantly different in those with NGT versus those with IGT or diabetes, with only occasional differences in those with IGT versus diabetes. In the state of NGT, there were differences among treatments in all CVD risk factors ($P < 0.001$), with the most favorable values noted in the ILS group. These treatment group differences per-

sisted in the IGT state, except for LDL cholesterol, but were mostly absent in those with diabetes.

Figure 1 summarizes mean changes in risk factors ordered according to the OGTT interval patterns. Overall, deterioration of glucose tolerance was associated with a worsening of risk factor levels, whereas improvement in status was associated with a beneficial risk factor change. The trend tests performed to assess relationships between the change in ordered categories of glucose tolerance and changes in CVD risk factors were statistically significant ($P < 0.001$ for all risk factors except for LDL-PPD [$P = 0.02$] in the ILS group and for HDL cholesterol [$P = 0.02$] in the placebo group).

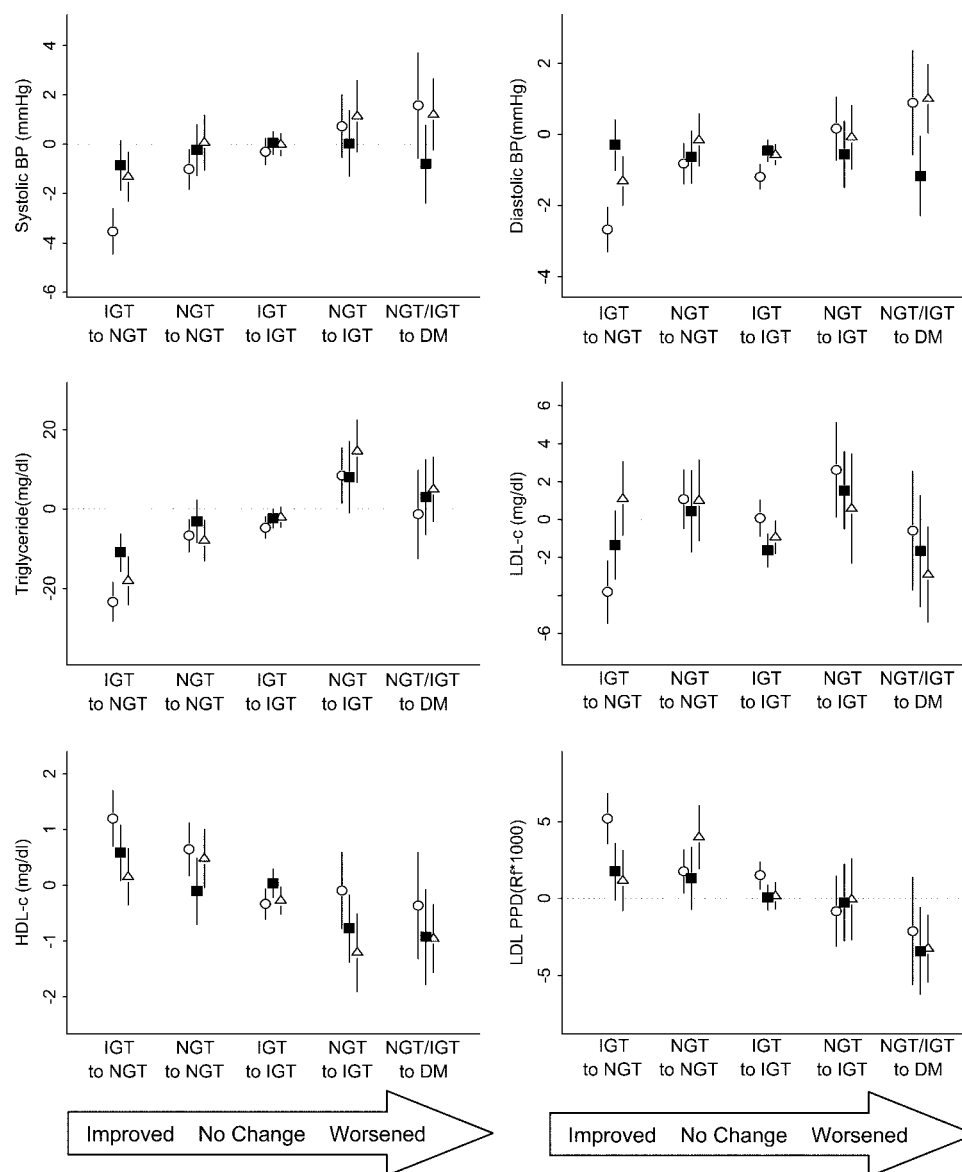


Figure 1—Mean interval change in cardiovascular risk factors by category of glucose tolerance interval change and by treatment group. The mean interval changes with their five 95% confidence limits for SBP, DBP, triglycerides, HDL cholesterol, LDL cholesterol, and LDL-PPD are arranged from left to right in each panel by treatment group, according to whether there was improvement in glucose tolerance status (IGT to NGT), maintenance of improvement (NGT to NGT), no change (IGT to IGT), deterioration back to baseline status (NGT to IGT), or conversion to diabetes (DM) (IGT/NGT to diabetes). ○, ILS group; ■, MET group; △, placebo group.

Improved glucose tolerance status

The largest changes are seen for transitions from IGT to NGT in the ILS group, where SBP and triglyceride fell by ~25%, whereas HDL cholesterol and LDL-PPD increased by ~8 and 17% of the baseline SD, respectively. The MET and placebo groups showed less significant improvements.

Unchanged glucose tolerance status

For IGT, risk factors showed little or no interval change across treatment groups, whereas for NGT, risk factor means improved slightly, mainly in ILS group, in

which SBP, DBP, and triglyceride levels fell ($P < 0.01$) by 7, 9, and 7% of baseline SD, respectively, while HDL cholesterol and LDL-PPD increased ($P < 0.05$) by 5 and 6% of baseline SD, respectively.

Worsening glucose tolerance status

Deterioration from NGT to IGT over 1 year manifested a slight increase in triglycerides for the ILS and placebo groups ($P < 0.05$). The mean HDL cholesterol change decreased slightly in the MET and placebo groups ($P < 0.05$), while LDL cholesterol slightly increased in the ILS group ($P < 0.05$).

Conversion to diabetes

Progression from IGT to diabetes in the ILS group was not associated with any significant change in risk factors. DBP increased in the placebo group by 1.0 mmHg ($P = 0.04$) but decreased in the MET group by 1.2 mmHg ($P = 0.04$), while HDL cholesterol and LDL-PPD fell in the placebo and MET groups ($P < 0.05$) and LDL cholesterol fell in the placebo group ($P < 0.02$).

Figure 2 expresses the mean risk factor change in relation to interval changes in fasting and 2-h glucose, BMI, and HOMA-IR in quartiles to assess relation-

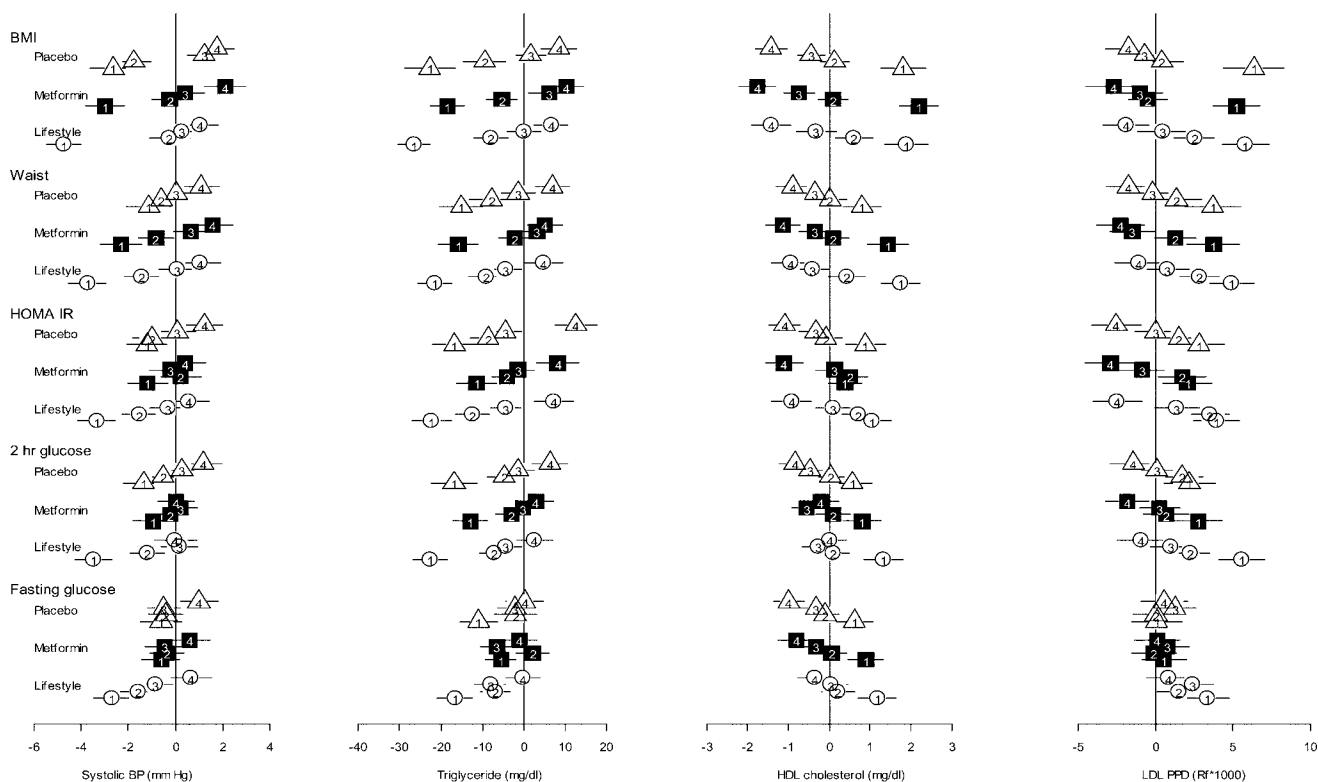


Figure 2—Mean cardiovascular risk factor interval changes adjusted for age, sex, and baseline risk factor values by quartiles of change in measures of glycemia and by treatment groups at 1-year intervals. The symbols and horizontal black line denote the mean change and 95% CI in selected cardiovascular risk factors for the three treatment groups: ○, ILS group; ■, MET group; △, placebo group. The numbers on the symbols correspond to the quartile of change in each of the measures of glycemia at 1-year intervals. The trend test across quartiles of glycemia showed a significant association (all $P < 0.01$) with SBP, triglycerides, HDL cholesterol, and LDL-PPD (except fasting glucose).

ships between risk factors and continuous measures of glycemia and to evaluate the extent to which BMI and HOMA-IR contributed to risk factor change. Overall SBP and triglyceride levels increased, and HDL cholesterol and LDL-PPD values decreased in the three intervention groups as a function of each measure of glycemia, BMI, and HOMA-IR. Fasting glucose tended to correlate less well with risk factor levels than did 2-h glucose or A1C. In mixed models, BMI and waist interval changes explained the effect of glycemia on SBP, and BMI only explained effects for LDL-PPD and attenuated those on HDL cholesterol, whereas HOMA-IR changes were found to have no influence.

CONCLUSIONS — This study shows that participants who developed diabetes trended toward higher blood pressure and triglycerides and lower HDL cholesterol and LDL-PPD levels than those who remained with IGT, while those whose OGTT reverted to normal had a significantly more favorable profile. These findings demonstrate that small changes in glycemia have a measurable effect on car-

diometabolic risk factors in subjects with IGT, although no such tendency was noted for LDL cholesterol, as previously noted (3). When risk factor changes were assessed over 1-year intervals in relation to OGTT status, favorable effects were again noted among those with improving glucose tolerance, while unfavorable trends accompanied deteriorating glucose tolerance.

Based upon differences in absolute risk factor levels as well as annual interval changes in those with IGT versus diabetes the incremental risk associated with progression to diabetes is modest. Using epidemiologic predictors of coronary heart disease risk, a reduction in HDL cholesterol of 0.02 mmol/l (0.78 mg/dl) and an elevation in SBP of 2 mmHg would predict an increase in event rates of 1.5–2.0% and 2–3% in events over 10 years, respectively (12,13). However, we found that risk factor values were associated with glycemic measures expressed as continuous variables, indicating that there is no unique effect of conversion to diabetes but rather a linear relationship between glycemic measures and risk factor levels,

as previously noted in cross-sectional studies (14). We found that quartiles of fasting glucose did not correlate as well with risk factors as did the 2-h glucose levels. This may reflect the narrow range of fasting glucose levels in our participants, although fasting glucose values may not correlate as well with CVD risk factors and events as do 2-h glucose values (4).

While there appeared to be little difference in risk factors between intervention groups in those who developed diabetes, for participants who remained with IGT or NGT, the risk factor profile among those in the ILS group was more favorable than the MET and placebo groups. Since fewer participants developed diabetes and more reverted to NGT in the ILS group compared with the other two interventions (5), our previous observation that the ILS group experienced less deterioration in the risk factor profile over time (15) is at least partially linked to the pattern of glucose tolerance responses to the interventions. The similarity of the risk factor profiles in participants who developed diabetes in the three groups

could also reflect a lack of success with the active interventions.

In the course of the DPP, 1,921 individuals reverted to NGT (39% in the ILS group and 23% in the placebo group). Reversion from IGT to NGT was associated with reductions in SBP, DBP, and triglycerides and increases in HDL cholesterol and LDL-PPD. This effect was significantly greater in the ILS group, where, in addition, LDL cholesterol levels fell and the estimated reduction in risk of heart disease predicted from epidemiologic assessments is 10–13% (12,13,16). This could again be partly explained by a more sizable improvement in glucose tolerance in the ILS group. Alternatively, other relevant effects of lifestyle change, such as weight reduction, increased physical activity, dietary changes, or improved insulin sensitivity were more substantial in the ILS group than the other groups (5) and should be greatest in those reverting to NGT. Furthermore, where participants maintained NGT for at least a year, there were further beneficial changes in risk factor levels, particularly in the ILS group, whereas worsening from NGT to IGT was associated with a significant deterioration in the risk profile. These findings suggest that reversion to NGT from IGT is associated with long-term improvement in risk factor status, which deteriorates rapidly if glucose tolerance worsens. Previous studies (17,18) have highlighted the importance of insulin resistance and weight change on CVD risk factors. This analysis indicates that BMI, but not insulin resistance, explains a significant proportion of the influence of glycemia on cardiometabolic risk, obliterating its effect on blood pressure and LDL-PPD but not on HDL cholesterol and triglycerides. This supports the concept that the increased cardiometabolic risk that accompanies deteriorating glucose tolerance likely reflects combined effects of elevated glucose levels and increasing weight, which are closely interrelated. In addition, the importance of these findings relates not only to future risk of CVD but also to the likelihood of the development of diabetes itself, since CVD risk factors were found to predict development of diabetes in pre-diabetic subjects independent of glycemic status (19).

In summary, this analysis demonstrates that progression from IGT to diabetes is associated with a small deterioration in the CVD risk factor profile in a manner that reflects a continuous relationship with glycemia and is independent of ILS or metformin interventions. These find-

ings indicate that biochemical conversion to diabetes from pre-diabetes has limited significance for CVD complications of diabetes, although sizable changes in glycemia may have greater effects (20). Together with longer duration of diabetes, this may explain why typically the risk factor profile is more unfavorable in subjects with diabetes than those with IGT (14). Importantly, improvement of glucose tolerance is associated with a more favorable risk factor profile, with ILS accompanied by larger improvements than metformin. Although the changes in CVD risk factors during the short period of follow-up in this study were small, they occur on a background of increased CVD risk (21), and their determinants may over time lead to a more substantial deterioration of cardiovascular risk in diabetic subjects. They therefore represent a target for prevention of CVD at an early phase in the development of diabetes.

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