Efficacy of Primary Prevention Interventions When Fasting and Postglucose Dysglycemia Coexist

Analysis of the Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2)

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OBJECTIVE — Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) have different pathophysiological abnormalities, and their combination may influence the effectiveness of the primary prevention tools. The hypothesis was tested in this analysis, which was done in a pooled sample of two Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2).

RESEARCH DESIGN AND METHODS — Researchers analyzed and followed up on the details of 845 of the 869 IGT subjects in the two studies for 3 years. Incidence of diabetes and its reversal to normoglycemia (normal glucose tolerance [NGT]) were assessed in group 1 with baseline isolated IGT (iIGT) (n = 667) and in group 2 with IGT + IFG (n = 178). The proportion developing diabetes in the groups was analyzed in the control arm with standard advice (IDPP-1) (n = 125), lifestyle modification (LSM) (297 from both), metformin (n = 125, IDPP-1), and LSM + metformin (n = 121, IDPP-1) and LSM + pioglitazone (n = 298, IDPP-2). Cox regression analysis was used to assess the influence of IGT + IFG versus iIGT on the effectiveness of the interventions.

RESULTS — Group 2 had a higher proportion developing diabetes in 3 years (56.2 vs. 33.6% in group 1, P = 0.000) and a lower rate of reversal to NGT (18 vs. 32.1%, P = 0.000). Cox regression analysis showed that effectiveness of intervention was not different in the presence of fasting and postglucose glycemia after adjusting for confounding variables.

CONCLUSIONS — The effectiveness of primary prevention strategies appears to be similar in subjects with iIGT or with combined IGT + IFG. However, the possibility remains that a larger study might show that the effectiveness is lower in those with the combined abnormality.

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Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) have a high potential to convert to type 2 diabetes. While an elevated basal hepatic glucose output and impaired early phase insulin secretion are the major abnormalities in IFG, IGT is characterized by more severe muscle insulin resistance (IR) and defects in late insulin secretion (1). Among Asian Indians, higher degrees of IR and β-cell dysfunction are seen in IFG than in IGT (2).

Analysis of six prospective studies among subjects with IGT showed that the incidence of diabetes varied widely from 23 to 62% within two to twenty-seven years of follow-up (3). The incidence was higher among populations with high prevalence of diabetes than in white populations. Incidence rates of diabetes in subjects with IFG or IGT or with a combined abnormality were varied in different populations (4–8).

Primary prevention studies have been done among subjects with IGT in different ethnic populations (9–14). Among these, only the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (12) recruited subjects with either isolated IFG (iIFG) or isolated IGT (iIGT) or both. Rosiglitazone was found to be a potent agent in preventing diabetes in this trial (12). The Diabetes Prevention Programme (DPP) (9) recruited subjects with a fasting glucose in the range of 5.3–6.9 mmol/l (95–125 mg/dl) and 2-h postglucose of 7.8–11 mmol/l (140–199 mg/dl) and nearly one-third of the participants had IFG by the present criteria (15).

Results of the Indian Diabetes Prevention Programme-1 (IDPP-1) showed that a moderate lifestyle modification (LSM) or a small dose of metformin (500 mg/day) reduced the risk of diabetes in a relatively nonobese but insulin resistant Asian Indian population (13). In the IDPP-2 study, we noted that pioglitazone did not improve the efficacy of LSM in Asian Indians (14). In both studies, subjects with persistent IGT and fasting glucose levels below 6.9 mmol/l were recruited. Therefore, some participants also had IFG. In view of the higher degree of biochemical abnormalities occurring when fasting and postprandial dysglycemia coexisted, it was considered important to study whether the combined abnormalities influenced the cumulative incidence of diabetes in comparison with subjects with iIGT. To increase the sample size, data from both IDPP studies were pooled. The participants’ baseline characteristics were identical in the two studies.

RESEARCH DESIGN AND METHODS — IDPP-1 and IDPP-2 were 3-year prospective, randomized controlled studies among Asian Indian subjects with persistent IGT (13,14). IDPP-1 had four groups: 1) control with standard advice, 2) LSM, 3) treated with metformin (500 mg/day), and 4) a combination of LSM and metformin (13).
IDPP-2 was done in a different cohort of IGT subjects using LSM and placebo as the control group and LSM and pioglitazone (30 mg/day) as the intervention group (14).

Sample selection for this analysis is shown in the flow chart in Figure 1 (Fig. 1). The two-stage selection procedure was used for recruiting reproducible IGT only. No case of isolated IFG was selected, and the presence of IFG was not an inclusion criterion.

In both studies the primary outcome was the development of diabetes detected by a standard oral glucose tolerance test (OGTT) (fasting plasma glucose \( \geq 7.0 \) mmol/l and/or 2-h post glucose \( \geq 11.1 \) mmol/l) (15). Reversal to normal glucose tolerance (fasting glucose <6.1 mmol/l and 2-h plasma glucose tolerance <7.8 mmol/l) was also considered as an outcome. All subjects underwent annual OGTT. A semiannual postprandial capillary glucose test was done. Diabetes detected in any person was confirmed with an OGTT.

In this study, the group with standard care from IDPP-1 was defined as the control group. The LSM group included LSM from IDPP-1 and the placebo group from IDPP-2. The effect of LSM drugs (metformin and pioglitazone) was analyzed since the numbers with IGT plus IFG were small in the individual drug group, and the outcome measures were present in numbers inadequate for statistical comparisons.

**Statistical analysis**

Means and SD are shown for normally distributed variables. Student t test was used for intergroup comparison. Median values were used for skewed variables, and Mann-Whitney U test was used for the comparisons. Intergroup proportions were compared using the \( \chi^2 \) test. Kaplan-Meier survival analysis was used to calculate the probability of cumulative incidence of diabetes in the groups.
Comparison of characteristics of study subjects with iIGT (group 1) and IGT + IFG (group 2)

Table 1—Comparison of characteristics of study subjects with iIGT (group 1) and IGT + IFG (group 2)

| Variables                                | Group 1          | Group 2          |
|-------------------------------------------|------------------|------------------|
| n (%)                                     | 667 (78.9)       | 178 (21.1)       |
| Men:Women                                 | 559:108          | 140:38           |
| Age (years)*                              | 45.5 ± 6.0       | 46.0 ± 5.8       |
| BMI (kg/m²)*                              | 25.7 ± 3.2       | 26.4 ± 3.8       |
| Waist circumference (cm)*                 | 89.6 ± 8.2       | 91.3 ± 8.4       |
| Blood pressure (mmHg)*                    |                  |                  |
| Systolic                                  | 120.4 ± 13.7     | 119.4 ± 12.5     |
| Diastolic                                  | 75.0 ± 9.6       | 75.6 ± 10.2      |
| Plasma glucose (mmol/l)*                  |                  |                  |
| Fasting                                   | 5.2 ± 0.6        | 6.4 ± 0.2**      |
| 30 min                                    | 9.4 ± 1.7        | 10.6 ± 1.7**     |
| 120 min                                   | 8.4 ± 1.0        | 9.1 ± 1.3**      |
| Plasma insulin (pmol/l)*                  |                  |                  |
| Fasting                                   | 108              | 114              |
| 30 min                                    | 480              | 420              |
| 120 min                                   | 618              | 612              |
| HOMA-IR†                                   | 4.2              | 5.5**            |
| δ I/G†                                     | 39.4             | 28.0**           |

*Means ± SD, †median values, **P = 0.000 vs. group 1.

RESULTS — Baseline characteristics of subjects in group 1 and group 2 are shown in Table 1. There was an excess of males in both the original studies; hence, an overrepresentation of men is also seen in this analysis. Subjects with combined abnormalities (group 2) had higher plasma glucose concentrations (P = 0.000), higher HOMA-IR, and lower δ I/G values than the subjects with iIGT (group 1) (P = 0.000).

Comparative analysis of the outcomes in the groups in 3 years is shown in Table 2 in relation to the interventions. In LSM + drug group, the incidence of diabetes was significantly lower in group 1 when compared with group 2 (P = 0.000). In group 1, LSM and LSM + metformin significantly reduced the incidence of diabetes and increased the reversal to normal glucose tolerance in relation to the control group (P = 0.000). In group 2, none of the intervention methods produced a significant benefit. The crude effect of all interventions on the incidence of diabetes appeared to be stronger among the subjects in group 1 (hazard ratio 0.547 [95% CI 0.400–0.747], P = 0.000) than in group 2 (0.792, [0.470–1.335], P = 0.382) when compared with the control group.

Table 2—Glycemic outcome up to 3 years in relation to interventions

| Outcome       | iIGT (group 1) | IGT + IFG (group 2) |
|---------------|----------------|---------------------|
| Control       |                |                     |
| n             | 99             | 26                  |
| NGT           | 14 (14.1)      | 4 (15.4)            |
| IGT           | 34 (34.3)      | 5 (19.2)            |
| Diabetes      | 51 (51.5)      | 17 (65.4)           |
| LSM           |                |                     |
| n             | 224            | 73                  |
| NGT           | 80 (35.7)*     | 15 (20.5)           |
| IGT           | 78 (34.8)      | 25 (34.2)           |
| Diabetes      | 66 (29.5)*     | 33 (45.2)           |
| Drug (metformin) |            |                     |
| n             | 106            | 19                  |
| NGT           | 29 (27.4)*     | 1 (5.3)             |
| IGT           | 36 (33.9)      | 4 (21.0)            |
| Diabetes      | 41 (38.7)      | 14 (73.7)           |
| LSM + drug    |                |                     |
| n             | 238            | 60                  |
| NGT           | 91 (38.2)*     | 12 (20.0)           |
| IGT           | 81 (34.0)      | 12 (20.0)           |
| Diabetes      | 66 (27.7)*     | 36 (60.0)**         |

Data are n (%). Intragroup comparison: *P = 0.000 vs. control, intergroup comparison: **P = 0.000.

CONCLUSIONS — In the Asian Indian subjects, the prevention strategies significantly decreased the cumulative incidence of diabetes in comparison with the control group both in the group with iIGT and in the group with IFG + IGT as shown by the Cox regression analysis. The crude effect of all interventions on the incidence of diabetes appeared to be
stronger among those with iIGT than those with IFG + IGT. However, a test of the interaction of the intervention effect by glycemic status was not statistically significant.

Among the primary prevention studies, the DPP (9) had nearly one-third of its participants having IFG by the present diagnostic criteria (15). In the placebo group, cumulative incidence of diabetes was more than threefold higher when the participants had basal fasting plasma glucose in the range of 6.1–6.9 mmol/l versus those who had lower values. In the former group, the relative risk reductions with interventions were also lower, more so with metformin (9).

In the DREAM trial, the annual conversion to diabetes in the placebo group was almost double in the participants with combined glycemic abnormalities than those with isolated abnormalities (12). However, the primary outcome with rosiglitazone was much the same, irrespective of the glycemic abnormality present at randomization.

We have not studied the effectiveness of pioglitazone in isolation. In our study, pioglitazone did not improve the effectiveness of LSM (14). It might be that LSM had produced the maximum possible benefit on the glycemic status, and hence no further improvement was seen by adding an insulin sensitizer (13,14).

The beneficial outcomes caused by the intervention strategies in the IDPP-1 occurred due to improved insulin action and insulin sensitivity. Subjects with higher baseline IR and/or low β-cell function had poor outcomes (18). It had been suggested that the differences in insulin sensitivity and insulin secretion between IGT and IFG and the greater severity of the abnormalities when both coexist might predict different rates of progression to diabetes, and different pharmacological agents might be needed to treat the pathophysiology (19).

Prospective studies in different populations have demonstrated higher rates of development of diabetes in subjects having combined IFG and IGT than in subjects having either of the glycemic abnormalities (4–6). The highest proportion of diabetes development among subjects with IFG and IGT (72.7%) was reported in a Brazilian Japanese population (7). Differences in follow-up periods and racial/ethnic differences among the study subjects account for the varied results.

The strength of the analysis lies in the prospective nature of our studies. By combining the results of two studies using different interventions, we could assess the impact of LSM and insulin sensitizers on the incidence of diabetes. However, the small sample sizes in the control and metformin groups posed some limitations. Moreover, due to the small numbers of subjects with combined IGT and IFG, the analysis could not be done separately in LSM + metformin and LSM + pioglitazone. The small number in group 2 might have influenced the results of univariate analyses.

**Table 3—Results of Cox regression analyses (dependent variable: diabetes)**

| Independent variable | β     | Hazard ratio | 95% CI     | P     |
|----------------------|-------|--------------|------------|-------|
| **Model 1**          |       |              |            |       |
| Intervention vs. control 1 | −0.5  | 0.61         | 0.47–0.80  | 0.000 |
| Group 2 vs. group 1   | 0.69  | 1.99         | 1.57–2.52  | 0.000 |
| **Model 2**          |       |              |            |       |
| Intervention vs. control | −0.60 | 0.55         | 0.40–0.75  | 0.000 |
| Group 2 vs. group 1   | 0.4   | 1.49         | 0.86–2.58  | 0.16  |
| Intervention vs. control × group 2 vs. group 1 | 0.36  | 1.44         | 0.78–2.64  | 0.24  |
| **Model 3**          |       |              |            |       |
| Age (years)          | 0.001 | 1.00         | 0.98–1.02  | 0.97  |
| Sex                  | −0.45 | 0.64         | 0.46–0.89  | 0.01  |
| BMI (kg/m²)          | 0.02  | 1.02         | 0.99–1.06  | 0.173 |
| HOMA-IR              | 0.01  | 1.01         | 0.97–1.05  | 0.65  |
| Intervention vs. control | −0.64 | 0.53         | 0.39–0.72  | 0.000 |
| Group 2 vs. group 1   | 0.32  | 1.38         | 0.78–2.43  | 0.27  |
| Intervention vs. control × group 2 vs. group 1 | 0.45  | 1.58         | 0.85–2.92  | 0.15  |

IDPP studies were originally designed to analyze the impact of prevention strategies in subjects with IGT. Subjects with isolated IFG were not selected, and we did not aim to confirm the presence of IFG in both steps of screening. The original IDPP cohorts had a male excess. Therefore, possible differences in the compliance to LSM among men and women could not be assessed.

In summary, interventions for the primary prevention of diabetes work effectively in subjects having either IGT or a combination of IGT + IFG. Although this study cannot confirm that the primary prevention of diabetes is more effective in people with iIGT than in those with IFG + IGT, the possibility remains that such an effect may become apparent in a larger study or a meta-analysis.

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