Efficacy of Primary Prevention Interventions When Fasting and Postglucose Dysglycemia Coexist

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

AMBADY RAMACHANDRAN, MD
NANDITHA ARUN, MD
ANANTH SAMITH SHETTY, MBBS, MDRC
CHAMUKUTTAN SNEHALATHA, DSC

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 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 were 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).

From the India Diabetes Research Foundation and Dr. A. Ramachandran's Diabetes Hospitals, Chennai, India.
Corresponding author: Ambady Ramachandran, ramachandran@vsnl.com.
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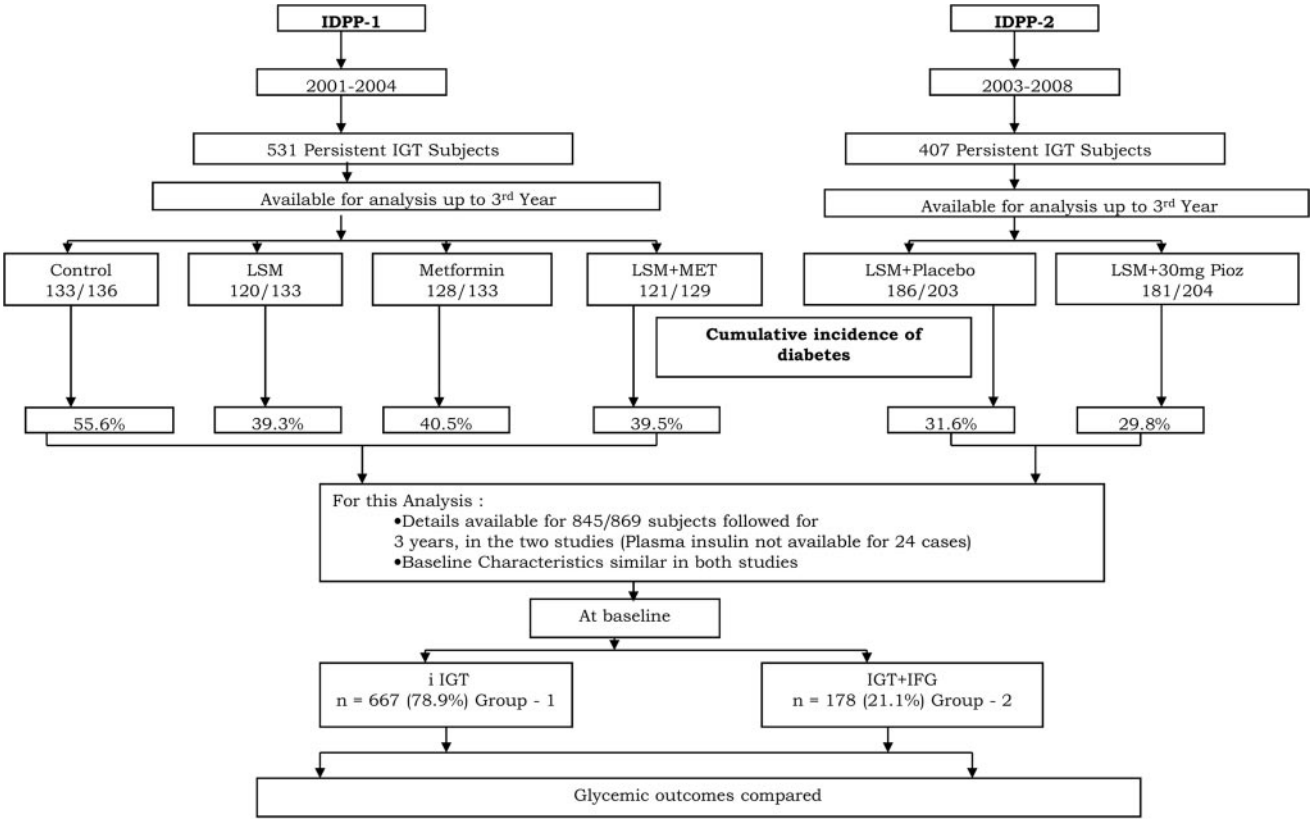

Figure 1—*The selection of original cohorts for the two studies, randomization, and the final outcome in the available subjects at the 3rd-year follow-up are shown. The selection criteria for this analysis and the baseline distribution of subjects in group 1 (iIGT) and group 2 (IGT + IFG) are also shown.*

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 ≥7.0 mmol/l and/or 2-h post glucose ≥11.1 mmol/l) (15). Reversal to normal glucose tolerance (fasting plasma 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 IDPP-1, in a median follow-up of 30 months, the relative risk reductions with the interventions were similar (28.5% with LSM, 26.4% with metformin, and 28.2% with LSM and metformin) when compared with the control group (13). In IDPP-2, the cumulative incidences of diabetes at 36 months were similar in the intervention (29.8%) and placebo groups (31.6%) (14).

BMI, waist circumference, and blood pressure were measured at baseline and during each review. Plasma glucose was measured (glucose oxidase method) at fasting, 30 min, and 2 h during the OGTT, and corresponding plasma insulin was measured using the radioimmunoassay kit of DiaSorin (Saluggia, Italy). Indexes of insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) (16) and early insulin secretion [(30-min fasting insulin [pmol/l]) ÷ 30-min glucose (mmol/l) (index of insulin secretion [δ I/G])] were calculated (17). Subjects from both studies having all the above measurements were included for this analysis. Among the total of 869 followed up for 3 years in both studies, data on plasma insulin was not available for 24 subjects. Hence this analysis was done using the data of 845 subjects. Group 1 was defined as having iIGT (2-h plasma glucose 7.8–11.0 mmol/l, 140–199 mg/dl) and group 2 as those with combined IFG (fasting 6.1–6.9 mmol/l, 110–125 mg/dl) and IGT. Data were available for 667 subjects in group 1 and 178 subjects in group 2 (Fig. 1).

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 + 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 χ^2 test. Kaplan-Meier survival analysis was used to calculate the probability of cumulative incidence of diabetes in the groups. Log-

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/m^2)*	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.

rank test was used for calculating *P* values. Cox proportional hazard model (enter method) was used to study the effect of independent variables on the incidence of diabetes. Initially, the crude effect of all interventions versus the control group was assessed separately by Cox regression analysis in group 1 and group 2. Three models were computed as follows. In the first model, all interventions versus the control group (reference) and group 2 versus group 1 (reference) were entered as independent variables. In the second model, the interaction of the two variables was also included. In the third model, the variables in the second model were included after adjusting for age (years), sex, BMI (kg/m^2), and IR. Fasting values of glucose and insulin were not included as HOMA-IR was calculated using these parameters. Statistical analyses were done using SPSS version 10.0 (SPSS, Chicago, IL). A *P* value of ≤0.001 was considered significant.

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 3 shows the results of the Cox regression models. The first model showed that the incidence of diabetes was reduced by the interventions. The effectiveness of intervention appeared to be significantly more in the iIGT group than in the group with IFG + IGT. The second model showed lack of interaction between the groups and intervention. The results were similar even after adjusting for age, sex, BMI, and IR. After adjusting for the confounding variables, the effectiveness of intervention did not differ between the two study groups.

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

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: **$P = 0.000$.

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/m^2)	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

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.

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 iIGT 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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