Early Improvement Predicts Reduced Risk of Incident Diabetes and Improved Cardiovascular Risk in Prediabetic Asian Indian Men Participating in a 2-Year Lifestyle Intervention Program

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OBJECTIVE

Objectives of this ancillary analysis of a prospective, prevention study among Asian Indians with impaired glucose tolerance (IGT) were *a*) to quantify the reduction in incident diabetes at 24 months in participants who achieved normal glucose tolerance (NGT) at 6 months (NGT-6 m) compared with the other participants, *b*) the factors influencing the reversal to NGT at the end of the study at 24 months (NGT-24 m), and *c*) to assess changes in cardiometabolic risk factors in different categories of dysglycemia at 24 months.

RESEARCH DESIGN AND METHODS

Data from a 2-year primary prevention trial were used. Effect of reversion to NGT-6 m on incidence of type 2 diabetes mellitus (T2DM) was analyzed using the Cox proportional hazards model. Predictive variables for reversal to NGT were identified using multiple logistic regression analysis. Changes in cardiometabolic risk factors were estimated according to the final glycemic status using fixed-effect, mixed-linear regression modeling.

RESULTS

The risk of T2DM in 2 years was lower by 75% in NGT-6 m group (hazard ratio 0.25 [95% CI 0.12–0.52]). Predictive variables for reversal to NGT-24 m were good baseline β-cell function (odds ratio [OR] 2.79 [95% CI 2.30–3.40]) and its further improvement (OR 5.70 [95% CI 4.58–7.08]), and NGT-6 m (OR 2.10 [95% CI 1.14–3.83]). BMI decreased in those who reverted to NGT. Deterioration to T2DM was associated with an increase in the levels of cardiometabolic risk factors.

CONCLUSIONS

Early reversion to NGT by lifestyle intervention in prediabetic men was associated with a significant reduction in subsequent incidence of diabetes. Good baseline β-cell function and its further improvement and NGT-6 m were associated with reversion to NGT-24 months. Reversion to NGT was associated with modest improvements, whereas conversion to T2DM was associated with significant worsening of the cardiometabolic risk profile.

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According to the current estimates by the International Diabetes Federation, ~21.5 million Asian Indians have prediabetes (impaired fasting glucose and/or impaired glucose tolerance [IGT]) (1). In addition to the risk of progression to type 2 diabetes mellitus (T2DM) (2–4), the prediabetic condition is often associated with increased levels of cardiometabolic risk factors, thereby increasing the risk for vascular complications that traditionally are attributed to diabetes (5).

Although reversal of prediabetes to normal glucose tolerance (NGT) is not uncommon (6,7), the effect of lifestyle intervention on reversal from persistent prediabetes to NGT has not been studied in detail in the Asian Indian population. In view of its potential importance of achieving NGT with the lifestyle intervention, the possible benefits of early reversal to NGT were explored in detail. Also, there have only been a few studies on the cardiovascular risk factors during the long-term outcome of prediabetes (8–10).

The aims of this ancillary cohort analysis of a prospective, prevention study among Asian Indians, with IGT were *a*) to quantify the risk reduction in incident T2DM during a 24-month follow-up in participants who achieved NGT at 6 months (NGT-6 m) compared with those who remained in the prediabetic state, *b*) to study the factors influencing the reversal of prediabetes to NGT, and *c*) to determine whether the cardiometabolic risk factors improved among those who reverted to NGT at the end of the study.

RESEARCH DESIGN AND METHODS

The flowchart (Fig. 1) describes the details of the selection of the participants for this ancillary analysis. The primary cohort consisted of 537 participants, all of whom received lifestyle advice at baseline. At 6 months, 473 individuals (88.1%) responded for the review; among them, 37 (7.8%) developed T2DM. Therefore, this analysis was done for the remaining 436 nondiabetic participants. They were classified into two groups by their glycemic status at 6 months: group 1, NGT-6 m if 2-h post-glucose (PG) value was <7.8 mmol/L; and group 2, IGT-6 m if the 2-h PG value was between 7.8 and <11.1 mmol/L. The analysis excluded individuals who met the criteria for T2DM (*n* = 37) and those who did not respond for the follow-up at 6 months (*n* = 64) and 24 months (*n* = 14). Therefore, this analysis was restricted to 422 participants (NGT-6 m: *n* = 126; IGT-6 m: *n* = 296) who were available for the final assessments at the end of the study.

The eligibility criteria, design, and methods of the study are reported in the primary paper (11). We could include only men in this study because it was done in workplaces and more than 96% of the employees were men. Briefly, Asian Indian men with IGT on two oral glucose tolerance tests (OGTT) were randomly assigned to the control group (*n* = 266), which received standard care advice on healthy diet and physical activity at baseline, or to the intervention group (*n* = 271), which in addition received frequent reminders about healthy lifestyle principles through mobile phone–based tailored text messages/short message service for 2 years. The control and intervention groups both received one-to-one, identical lifestyle advice, the groups being distinguished solely by whether they received reinforcement of lifestyle advice by short message service. The study showed for the first time that motivation through text messaging could help reduce the incidence of T2DM (11). The study protocol was approved by the India Diabetes Research Foundation Ethical Review Committee, Chennai, India, and the participants gave written informed consent before enrollment in the study.

Because the main objective of this post hoc analysis was to assess the benefits of early reversal to NGT on incident T2DM and because both groups were advised on lifestyle changes, we considered both groups as a single cohort for this analysis. The participants were assessed at 6-month intervals for 2 years to ascertain their glycemic status. The OGTT with blood sampling at three intervals (fasting, 30 min, and 120 min) was done at annual visits. At the interim visits (6 and 18 months), only a 2-h PG load test was done to minimize the inconvenience to the participants. If the glucose value was 11.1 mmol/L or greater, a 2-h OGTT was done within 1 week.

The primary outcome of the study was the development of T2DM as classified by the World Health Organization (WHO) recommendations (12) as a fasting plasma glucose of 7.0 mmol/L or higher and/or 11.1 mmol/L or higher 2 h after a 75-g oral glucose load.

Anthropometric, hemodynamic, and biochemical variables were estimated by standard procedures (11). Blood pressure was measured (mean of two readings) at each visit using a sphygmomanometer. Height and weight were measured to the nearest 0.1 cm and 0.5 kg, respectively, and BMI was calculated. Waist circumference was measured midway between the lower rib margin and the iliac crest using a measuring tape to the nearest 0.1 cm.

Venous blood samples collected at OGTT were processed according to standard procedures (11). The samples were frozen at −20°C until the biochemical and insulin assays were done. Plasma glucose (hexokinase method, coefficient of variation <3%; detection range: 0.11–25 mmol/L) was measured in a Roche/Hitachi 911autoanalyzer. Lipid profile was measured in serum using standard enzymatic methods at baseline and at annual visits. Triglycerides, total cholesterol, and HDL cholesterol were measured on the Roche/Hitachi 911 clinical analyzer. Plasma insulin was measured at fasting and at 30 and 120 min using an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany; coefficient of variation <3%; detection range: 1.39–6,945 pmol/L) on the Elecsys analyzer. Assessments of the participant's dietary energy intake and physical activity levels were made using validated questionnaires used in our previous diabetes prevention programs (11,13).

HOMA insulin resistance (HOMA-IR) (14) was calculated using the formula: [fasting insulin (pmol/L) × fasting glucose (mmol/L)]/22.5. The insulinogenic index was calculated as the ratio of the change in insulin from 0 to 30 min to glucose at 30 min after the OGTT ($\Delta Insulin_{0-30}/Glucose_{30}$) (15). The Matsuda insulin sensitivity index (ISI) was calculated by the following formula: [$10^4/\sqrt{}$(fasting glucose × insulin) × (mean OGTT glucose × mean OGTT insulin)], with mean glucose and insulin calculated from values at fasting, 30 min, and 120 min of the OGTT test (16). Total area under the curve (AUC) for insulin and for glucose were calculated using the trapezoidal rule, and a ratio of the two was calculated ($AUC_{insulin\text{-}to\text{-}glucose}$).

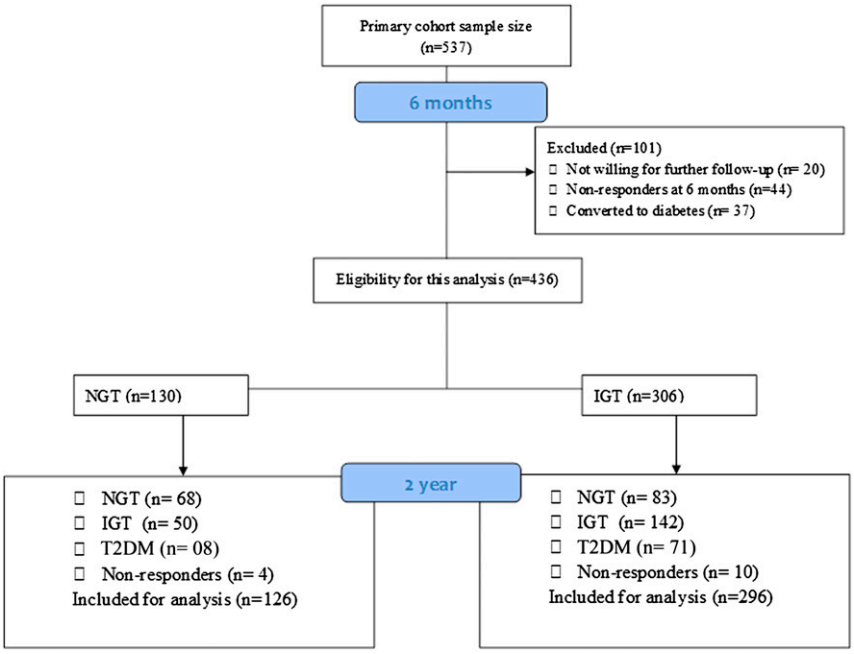


Figure 1—Study design and participants' flow for this analysis. Diagnosis is based on WHO criteria.

Among the different combinations of insulin secretory and sensitivity measures, the product of the $AUC_{insulin\text{-}to\text{-}glucose}$ and ISI displayed hyperbolic relationship characteristics of the disposition index (17). We have noted that the disposition index was the most sensitive index among the surrogate measures analyzed using receiver operating characteristic curve analysis. Hence, this measure was used as the measure of β-cell secretion relative to the prevailing insulin sensitivity.

Statistical Analysis

Glycemic status was assessed by OGTT using the WHO criteria (12). Comparisons between groups were done using the χ^2 test after adjustment with Bonferroni *P* value correction for qualitative variables. One-way ANOVA following Bonferroni post hoc correction for the normally distributed variables and the nonparametric Kruskal-Wallis test with the Dunn multiple comparison test were used for highly skewed variables. Incidence of T2DM at the end of 24 months was compared using the Cox proportional hazards model between those who reverted to NGT and those who had remained in the prediabetic state at 6 months. Kaplan-Meier survival curves were computed to estimate the probability of remaining free of T2DM in the two groups. The number of participants who progressed to T2DM during the entire study period was expressed as incidence per 100 person-years. Person-years were the sum of time under follow-up for all participants in a group before the diagnosis of diabetes or at the end of follow-up if diabetes did not develop during the time of interest. Multiple logistic regressions modeling (odds ratio [OR]) with the forward conditional method was used to identify significant predictors for reversion to NGT at the end of the study. For continuous variables, the OR (95% CI) per 1 SD increase in the predictor was calculated, and for categorical variables, the OR (95% CI) was calculated as the ratio between each category and the reference group. Changes in variables were computed by subtracting the final values (or at the time of diagnosis of diabetes) from baseline. Variables included were age, treatment group, family history of diabetes, baseline 2-h PG, baseline and change in BMI, HOMA-IR, insulinogenic index, dietary energy intake, and physical activity. In a separate model, the oral disposition index was included, and HOMA-IR, insulinogenic index, and 2-h PG were excluded. The data of the second model are shown. Also included was NGT-6 m.

The relationship of reversal to NGT or conversion to T2DM at the end of the study and cardiometabolic risk factors were assessed using fixed-effect, mixed-linear regression modeling with maximum likelihood parameter estimation for continuous variables. The reference was the IGT group, and the comparators were the NGT and the T2DM groups. Differences in the estimated marginal means between the groups with 95% CIs are reported. Because the objective was to evaluate changes in cardiometabolic risk factors at the end of the second year, only baseline and values at 2 years were included in the analysis. All analyses were performed using IBM SPSS19.0 software (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics of the participants who underwent the final review (n = 459) stratified by 6-month glycemic status are presented in Table 1. Participants in NGT-6 m were older compared with those in IGT-6 m. Measures of adiposity, blood pressure, lipid profile, energy intake, physical activity levels, and HOMA-IR were similar among the groups. Baseline levels of 2 h PG were higher ($P < 0.0001$), and the values of insulinogenic index ($P = 0.019$) and β-cell compensation (disposition index; $P < 0.0001$) were lower among those who developed T2DM at 6 months compared with the other groups.

At 6 months, the mean (interquartile range [IQR]) percentage weight loss was higher in NGT-6 m compared with IGT-6 m (−1.2% [IQR −3.5 to 1.4] vs. −0.2% [IQR –2.4 to 1.8]; $P = 0.023$). Correspondingly, BMI was lower in the NGT-6 m than in the IGT-6 m group (estimated marginal mean difference: −0.40 [95% CI −0.63 to −0.16]; $P = 0.001$). The energy intake (kcal) was also lower in NGT-6 m than in IGT-6 m (estimated marginal mean difference: −64.1 [95% CI −98.0 to −30.2]; $P < 0.0001$). Physical activity levels did not improve in either group (0.162 [95% CI −1.28 to 1.60]; P = 0.825) at 6 months.

At the end of the study, 79 of the 422 participants (18.7%) developed T2DM (NGT-6 m: 8 of 126 [6.3%]; IGT-6 m: 71 of 296 [24.0%]). The probability of remaining free of T2DM in the two groups calculated using Kaplan-Meier survival curves is shown in Fig. 2. Incidence rates per 100 person-years were 0.9 (95% CI

Table 1—Baseline characteristics of participants who completed the final follow-up categorized by glycemic status at 6 months' follow-up

Variables	NGT-6 m (*n* = 126)	IGT-6 m (*n* = 296)	T2DM-6 m (*n* = 37)	*P* value
		n (%)		
Family history	69 (54.8)	156 (52.7)	22 (59.5)	0.716
Smoking	30 (23.8)	60 (20.3)	10 (27.0)	0.522
Alcohol consumption	42 (33.3)	116 (39.2)	10 (27.0)	0.235
Hypertension	29 (23.0)	82 (27.7)	8 (21.6)	0.497
		Mean ± SD or median (IQR)		
Age (years)	47.2 ± 4.8	45.7 ± 4.6*	46.3 ± 4.4	0.012
BMI (kg/m^2)	25.6 ± 3.2	25.7 ± 3.0	26.2 ± 3.4	0.637
Waist circumference (cm)	92.0 ± 6.7	92.4 ± 7.0	93.0 ± 7.4	0.743
Blood pressure (mmHg)				
Systolic	124.1 ± 14.7	122.6 ± 13.4	121.1 ± 12.1	0.435
Diastolic	79.9 ± 9.1	80.1 ± 8.2	80.7 ± 7.7	0.887
Plasma glucose (mmol/L)				
Fasting	5.6 ± 0.5	5.6 ± 0.5	5.7 ± 0.6	0.265
2 h	8.6 ± 0.8	8.8 ± 0.8	9.4 ± 0.9§#	<0.0001
Lipid profile (mmol/L)				
Cholesterol	4.9 ± 0.9	4.9 ± 0.9	4.8 ± 1.1	0.990
Triglycerides	1.6 (1.1–2.3)	1.6 (1.2–2.1)	1.8 (1.3–2.4)	0.394
HDL cholesterol	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.705
HOMA-IR	2.9 ± 1.2	3.1 ± 1.3	3.4 ± 0.8	0.065
Insulinogenic index	50.5 (30.8–83.7)	49.3 (31.0–78.5)	36.5 (24.0–59.7)‡##	0.019
Disposition index	161.3 (124.3–194.7)	154.9 (125.2–186.5)	121.9 (103.9–139.2)§#	<0.0001
Dietary energy intake (kcal)	2,128 ± 288	2,097 ± 282	2,126 ± 259	0.548
Physical activity score	35 (18–46)	36 (30–56)	42 (34–65)	0.094

Data are expressed as mean ± SD for normally distributed variables and analyzed using one-way ANOVA after Bonferroni correction, as counts (percentages) for qualitative variables and analyzed by χ^2 test after adjustment with Bonferroni *P* value correction, and as median (IQR) for nonnormally distributed variables and analyzed using the Kruskal-Wallis test with the Dunn multiple comparison test. *$P < 0.05$ NGT vs. IGT. ‡$P < 0.05$ IGT vs. T2DM. §$P < 0.01$ IGT vs. T2DM. #$P < 0.01$ NGT vs. T2DM.

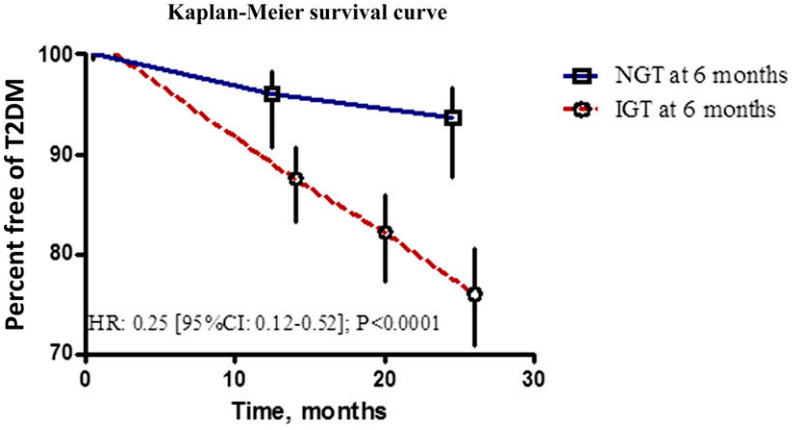
0.1–1.7) in NGT-6 m and 8.0 (95% CI 5.7–10.2) in IGT-6 m. The Cox proportional hazards model showed that participants who displayed early reversion to normoglycemia had a 75% lower risk of T2DM at the end of 24 months (hazard ratio 0.25 [95% CI 0.12–0.52]; $P < 0.0001$).

Multiple logistic regression analysis with NGT-24 m vs. dysglycemia (prediabetes and diabetes) as the dependent variable showed that the baseline oral disposition index (OR 2.79 [95% CI 2.30–3.40]; $P < 0.0001$) and its further improvement (OR 5.70 [95% CI 4.58–7.08; $P < 0.0001$) and NGT-6 month status (OR 2.10 [95% CI 1.14–3.83]; $P = 0.017$) were the significant predictors of NGT-24 m (Table 2). Although the mean age of the NGT-6 m group was older than the IGT-6 m group (Table 1), age was not a significant contributor of regression to the NGT-24 m group. The association of the baseline insulinogenic index (OR 1.63 [95% CI 1.43–1.86]), change in the insulinogenic index (OR 1.35 [95% CI 1.22–2.41]), 2 h PG (OR 0.65 [95% CI 0.57–0.73]), and change in BMI (OR 0.55 [95% CI 0.48–0.63]) was lower than that of the oral disposition index (data not shown).

Table 3 reports the changes in cardiometabolic variables according to the final glycemic categories. The data were analyzed by fixed-effect, mixed linear modeling between the baseline and the end of the study. Overall, progression of IGT to T2DM was associated with raised systolic (mean change 3.3 [95% CI 0.41–6.2]; $P = 0.025$), and diastolic blood pressure (mean change: 2.28 [95% CI 0.24–4.32]; $P = 0.024$), cholesterol (mean change: 0.331 [95% CI 0.090–0.572]; $P = 0.004$), and triglyceride (mean change: 0.206 [95% CI 0.031–0.381]; $P = 0.021$) levels compared with individuals who remained at the prediabetic state. Reversion to NGT was associated with decreased BMI compared with IGT remainders (mean change: −0.406 [95% CI −0.676 to −0.136]; $P = 0.002$).

CONCLUSIONS

This prospective study in Asian Indian prediabetic men showed that remission to NGT within a short period of lifestyle intervention was associated with a 75% lower incidence of T2DM in 24 months compared with the remaining dysglycemic participants. This observation highlights the benefit of identification of the prediabetic state and early intervention with lifestyle changes. The novelty of our observation lies in the fact that the benefits were seen in Asian Indians with specific adverse biological characteristics, such as high levels of insulin resistance at relatively lower BMI, which predispose them to develop diabetes at a younger age. The significant reduction in the incidence of T2DM at the end of the study could have been partly due to the benefits related to the early reversal to normoglycemia in many participants. The long-term benefit of achieving NGT at least once in the course of an intervention was demonstrated in the Diabetes Prevention



Cumulative incidence of diabetes

Glycemic status at 6 months	Time, months			
	6	12	18	24
Normal glucose tolerance (n)				
At risk	130	122	113	118
Converted to diabetes	--	5	5	8
Impaired glucose tolerance (n)				
At risk	306	260	224	225
Converted to diabetes	--	37	53	71

Figure 2—Early reversion to NGT and the probability of remaining free of T2DM at the end of the study. The error bars show 95% CIs. Eligibility was assessed according to WHO criteria. HR, hazard ratio.

Program Outcomes Study (18), which showed that reversion to normal glucose regulation, even if transient, was associated with a 56.0% relative risk reduction in developing diabetes versus those who consistently had prediabetes.

The factors responsible for the restoration of NGT at the end of the study were *a*) better baseline oral disposition index, *b*) improvement in oral disposition index, and *c*) early reversion to NGT. This finding underscores that prevention of diabetes and reversal to NGT are primarily through preservation of β-cell function, as shown in our earlier prevention programs (19). Similar observations have been reported in the Diabetes Prevention Program (20) and the Finnish Diabetes Prevention Study (21). Several multiethnic studies reported that the prevalence of insulin resistance in South Asian populations was three- and fourfold higher, coupled with compromised β-cell function, compared with Caucasian populations (22).

A novel observation was that benefits of intervention could be obtained with modest reductions in weight, unlike in the Western studies in which the benefits had been largely attributed to significant weight reduction (23,24). The relationship between dysglycemia and obesity is rather a complex phenomenon and seems to be modified by ethnicity (25). For a given range of BMI, the age-matched, apparently healthy Asian Indians were more insulin-resistant, had reduced insulin clearance rates, higher insulin levels, and poorer lipid profiles (26). Beneficial effects associated with restoration of NGT were independent of group allocation. The present results demonstrate that lifestyle intervention promotes beneficial changes leading to early reversal to NGT, which, even if transient, has the potential to prevent diabetes. Early reversal to NGT was also associated with improved cardiovascular risk factors. Probably, those with favorable biochemical features reverted to NGT, which might have been independent of the benefits of specific intervention, during the short period.

The present analysis confirmed that the improvement of glucose tolerance was associated with a favorable cardiometabolic risk profile, whereas conversion to diabetes resulted in deterioration of risk factors. This finding is particularly important because prediabetes is not a benign condition. A meta-analysis of 38 prospective studies demonstrated that dysglycemia was associated with increased risk of developing cardiovascular disease (relative risk 27% [95% CI 9%–48%]) (5). Therefore, an early and effective lifestyle intervention among high-risk subjects is the need of the hour to reduce the global burden of diabetes and associated complications. The beneficial effects of lifestyle intervention on cardiovascular disease risk factors were demonstrated after 1 year in the Look AHEAD (Action for Health in Diabetes) study using intensive lifestyle intervention (27). Recently, the 23-year follow-up of the Da-Qing study demonstrated that a 6-year lifestyle intervention in Chinese people with IGT could significantly reduce the long-term outcome of cardiovascular and all-cause mortality in addition to a reduction in the incidence of diabetes (28).

Our study has a few limitations. The study cohort did not include women; therefore, the beneficial effects of early reversal to NGT on incident T2DM needs further evidence from a female cohort.

Table 2—Predictors of regression to NGT at the end of the study (NGT-24 m)

Variables (per SD)	OR (95% CI)	*P* value
Oral disposition index ($AUC_{insulin\text{-}to\text{-}glucose}$ × ISI) − baseline (per 48.9)	2.79 (2.30–3.40)	<0.0001
ΔOral disposition index ($AUC_{insulin\text{-}to\text{-}glucose}$ × ISI) (per 72.5)	5.70 (4.58–7.08)	<0.0001
NGT-6 m	2.10 (1.14–3.83)	0.017

Multiple logistic regression analysis with stepwise conditional addition; dependent variable: regressors (NGT-24 m) vs. nonregressors (dysglycemia). Nonsignificant variables: age (years, continuous), group (standard care advice/intervention), family history of diabetes (yes/no), baseline BMI (continuous), change in BMI, energy intake (kcal, continuous), change in energy intake (kcal, continuous), baseline physical activity (score, continuous), and change in physical activity levels (score, continuous).

Table 3—Mean interval change in cardiometabolic risk variables by category of glucose tolerance at the end of the study

Variables	Baseline	Final	Estimated marginal mean difference	*P* value
BMI (kg/m^2)				
IGT to NGT	25.8 ± 3.0	25.4 ± 3.1	−0.406 (−0.676 to −0.136)	0.002
IGT to IGT	25.4 ± 2.9	25.4 ± 3.0	Ref	Ref
IGT to T2DM	26.1 ± 3.6	26.3 ± 3.9	0.227 (−0.105 to 0.559)	0.249
Waist circumference (cm)				
IGT to NGT	92.5 ± 6.7	91.6 ± 7.2	−0.987 (−2.062 to 0.088)	0.079
IGT to IGT	91.8 ± 6.5	92.0 ± 7.2	Ref	Ref
IGT to T2DM	93.2 ± 8.1	94.5 ± 9.1	1.206 (−0.115 to 2.527)	0.081
Systolic BP (mmHg)				
IGT to NGT	123.7 ± 13.0	119.3 ± 11.8	1.27 (−1.09 to 3.62)	0.288
IGT to IGT	121.7 ± 13.9	117.3 ± 11.5	Ref	Ref
IGT to T2DM	125.1 ± 15.1	121.9 ± 14.1	3.3 (0.41−6.2)	0.025
Diastolic BP (mmHg)				
IGT to NGT	80.0 ± 8.1	77.4 ± 7.3	0.50 (−0.947 to 1.95)	0.496
IGT to IGT	80.0 ± 8.2	76.7 ± 6.8	Ref	Ref
IGT to T2DM	81.6 ± 9.7	79.6 ± 7.9	2.28 (0.24−4.32)	0.024
Cholesterol (mmol/L)				
IGT to NGT	4.9 ± 0.9	4.7 ± 0.8	−0.08 (−0.277 to 0.115)	0.708
IGT to IGT	4.9 ± 0.9	4.8 ± 1.0	Ref	Ref
IGT to T2DM	4.9 ± 0.9	5.1 ± 1.0	0.331 (0.090−0.572)	0.004
HDL cholesterol (mmol/L)				
IGT to NGT	0.92 ± 0.23	0.96 ± 0.20	0.012 (−0.03 to 0.053)	0.955
IGT to IGT	0.89 ± 0.18	0.93 ± 0.20	Ref	Ref
IGT to T2DM	0.87 ± 0.19	0.97 ± 0.22	0.031 (−0.021 to 0.083)	0.358
Triglycerides (mmol/L)				
IGT to NGT	1.61 (1.13–2.15)	1.45 (1.11–1.91)	−0.158(−0.300 to 0.015)	0.055
IGT to IGT	1.52 (1.16–2.01)	1.50 (1.14–2.08)	Ref	Ref
IGT to T2DM	1.80 (1.32–2.40)	1.66 (1.30–2.60)	0.206 (0.031−0.381)	0.021

Data are mean ±SD or median (IQR). BP, blood pressure. We used fixed-effect, mixed-linear regression modeling with maximum likelihood parameter estimation groups to generate estimated marginal means and difference in mean change (95% CI) at the end of follow-up. The reference was the IGT to IGT group (n = 151), and the comparators were the IGT to NGT (n = 192) and the IGT to T2DM (n = 79). Post hoc analysis was by Bonferroni correction.

The follow-up duration was fairly short; nevertheless, the long-term benefits of attaining NGT on incident T2DM was seen over 9 years in the Diabetes Prevention Program Outcomes Study cohort (18). Finally, we did not measure fasting plasma glucose levels at 6 months, and classification of glycemic status was solely based on 2-h PG values, except in diabetic case subjects, who had a confirmatory three-sample OGTT. Thus, misclassification might have occurred in a small percentage.

In summary, the important observation of the analysis was that reversal to NGT, even within 6 months of lifestyle intervention, had sustained benefit on the metabolism, with a marked reduction in the overall incidence of diabetes. It was also demonstrated that minimum weight reduction, presence of good baseline β-cell function, and its further improvement during the intervention facilitated better glycemic outcomes. This analysis also demonstrated that improvement of glucose tolerance was associated with a favorable cardiometabolic risk profile, whereas deterioration to T2DM was associated with adverse changes. Reduction in atherogenic risk factors in prediabetic individuals could lead to better cardiovascular outcomes over long periods. Long-term follow-up studies are required for better understanding of the mechanisms causing early reversal to NGT and its sustainability in Asian Indians.

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