ORIGINAL ARTICLE

Incidence of Type 2 Diabetes is Higher among Men with Persistent Impaired Glucose Tolerance than in Transient Impaired Glucose Tolerance – A 5 year Follow up Study

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Abstract

Objective: This was a 5 year comparative analysis of the incidence of type 2 diabetes in men who had persistent impaired glucose tolerance (P-IGT) versus transient impaired glucose tolerance (T-IGT). P-IGT (positive IGT on two oral glucose tolerance tests (OGTT), T-IGT (IGT in first OGTT and normal glucose tolerance (NGT) in the 2nd OGTT).

Methods: The samples were collected from a randomized controlled diabetes prevention study. The prevention study was done using lifestyle modification (LSM) promoted by use of mobile short message services (SMS) for 2 years. The control group of the randomized study who received advice on LSM at only the baseline formed the P-IGT group for the 3 years follow up study (n=236). T-IGT (n=569) were available from those who had NGT on the 2nd OGTT while screening for the prevention study. The total diabetes incidence at 5 years in the study groups were compared using standard OGTT (WHO criteria).

Results: The conversion rate to diabetes in 5 years was significantly lower among T-IGT than among P-IGT, OR=0.202 (95% CI, 0.145-0.296,p<0.0001). P-IGT had higher rate of risk factors for diabetes than T-IGT.

Conclusion: The risk of conversion to diabetes was 80 percent lower in T-IGT than in P-IGT. Identification of P-IGT will help in selecting persons who require early intervention for diabetes.

Introduction

Impaired glucose tolerance (IGT) is an intermediate stage of hyperglycaemia which carries a high risk for type 2 diabetes and also its complications. Identification of people with prediabetes is of great importance, as accumulating evidence demonstrate that the progression to clinical diabetes can be prevented by lifestyle changes or by use of some pharmacological agents such as metformin.[1,2] Lifestyle modification (LSM) is found to be a practical, acceptable and a safe method of preventing diabetes[3] and a few studies[4] also show benefits on reducing cardiovascular risk factors.

In the Indian Diabetes Prevention Programmes[5,6] we have shown that LSM is effective in Asian Indians with persistent IGT (P-IGT) (Persons showing IGT on two oral glucose tolerance tests (OGTT)). During the screening process, a large number of persons with transient IGT (T-IGT) were identified, ie presence of IGT in the first OGTT and normoglycaemia(NGT) was detected on a repeat OGTT within a week. They were advised to follow healthy diet and improved physical activity, but were not followed, as a part of the trial.

The risk of diabetes among the T-IGT is not known. The objective of this analysis was to find out the incidence of diabetes in men with T-IGT in comparison with the conversion rate in a cohort of P-IGT in 5 years.

Materials and Methods

Participants: Selection of the study participants is shown in the flow chart (Figure 1). For the present analysis, we have used data from a cohort of men with IGT who were evaluated for inclusion in a randomized controlled primary prevention trial on diabetes in India.[6] Non-diabetic men (n=8741, aged 35-55 years) were screened from August 2009 to November 2010. During this initial screening, IGT was detected in 2744 participants by a capillary blood glucose measurement with a glucometer after a 75 gm oral glucose load (140-199 mg/dl) (7.8-11.0 mmol/l). Of these, 1832 participants were invited to undergo a 2nd confirmatory OGTT within a week. Among the 1369 IGT subjects who responded, 537 had persistent IGT (positive IGT on two OGTTs (P-IGT)) and were recruited for the diabetes prevention trial[6]. Another 720 had normal 2h value (<140mg/dl, <7.8 mmol/l) and were referred to as having transient IGT (T-IGT). They were advised standard lifestyle practices although they were not recruited for the prevention trial. They were not contacted for the next 5 years. At the end of 5 years they were invited for a follow up analysis. Between August and December 2015,

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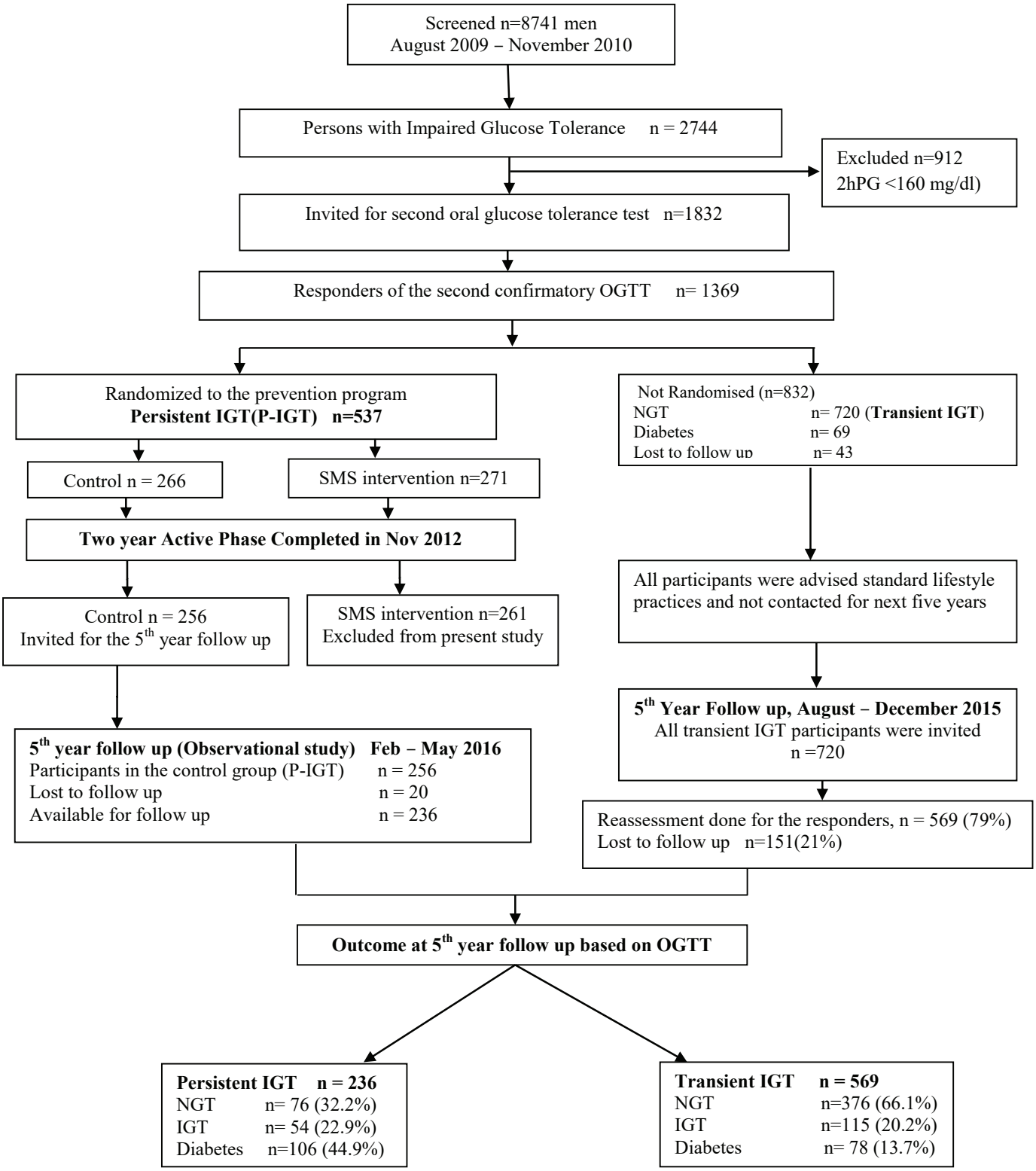

NGT- Normal Glucose Tolerance, OGTT- Oral Glucose Tolerance Test, IGT – Impaired Glucose Tolerance, 2hPG- 2h Post glucose, SMS-Short Message Services

Fig. 1: Flow chart showing the details of sample selection of the study groups and the outcome at the 5th year assessment

T-IGT participants (n=720) were invited to undergo an OGTT with clinical assessment to ascertain the incidence of dysglycemia. Among the 720 subjects with T-IGT, data was available for 569 (79%) at the end of 5th year. The follow up was done in person for 408 and the data were collected for 161 from their medical records.

Subjects with P-IGT were randomized in two groups, the control and the intervention groups. The control group received advice on healthy lifestyle practices at the baseline and during the 6 monthly clinical assessment visits

Table 1: Comparative analysis of the baseline and follow up values of anthropometry and biochemical parameters in the study groups

Variables	P-IGT						T-IGT					
		Baseline		Follow up		Intra Group		Baseline		Follow up		Intra Group
	n	Mean	SD	Mean	SD	P value	n	Mean	SD	Mean	SD	P Value
Weight (kg)	236	71.9	9.5	72.7	9.8	0.002	569	72.5	10.4	72.7	10.7	0.240
Body mass index (kg/m^2)	236	25.8	3.0	26.0	3.2	0.014	569	25.9	3.1	26.0	3.3	0.184
Waist circumference (cm)	149	92.7	7.5	94.2	7.6	<0.0001	379	91.5[#]	8.0	93.7	8.8	<0.0001
Plasma glucose (mg/dl)												
0 min	222	101.9	9.6	108.8	20.9	<0.0001	569	96.5[†]	8.7	101.4[†]	18.3	<0.0001
30 min	180	177.9	29.1	157.6	65.1	<0.0001	385	162.9[†]	28.0	169.5[$]	29.5	<0.0001
120 min	205	159.7	15.3	175.7	44.4	<0.0001	429	111.2[†]	16.9	146.8[†]	44.3	<0.0001
Lipid profile (mg/dl)												
Cholesterol	213	189.2	36.9	188.7	33.3	0.780	556	186.25	36.9	186.1	36.2	0.967
Triglycerides[*]	197	146 (108 – 201)		155 (120-217)		0.01	469	138 (102 – 184)[#]		140(106 – 202)		0.001
HDL-cholesterol	197	34.8	7.1	37.6	7.8	<0.0001	465	34.6	8.5	38.8	8.8	<0.0001

[*]Median (Interquartile Range); T-IGT Vs P-IGT , P values; Data are mean ± SD (values were compared using paired and unpaired Student's t-test) or medians (comparisons were done using Wilcoxon Signed Rank test and Mann Whitney U test); [#]Baseline waist circumference=0.042; [#]Baseline TG=0.045; [†]Baseline Plasma glucose 0 min, 30 min, 120 min <0.0001; [†]Follow up Plasma glucose 0 min, 120 min <0.0001; [$]Follow up Plasma glucose 30 min=0.003

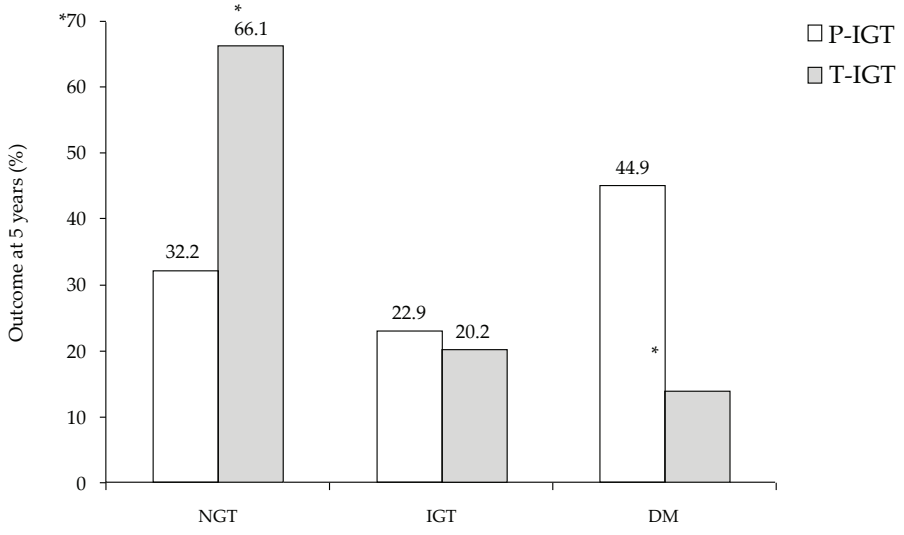

Fig. 2: Glycaemic outcome at the end of 5 years in the study groups. *P-IGT Vs T-IGT; NGT – χ^2=76.385, p<0.0001, Diabetes – χ^2=90.372, p<0.0001

for 2 years. The intervention group received mobile phone messages (SMS) on lifestyle practices regularly for 2 years in addition to the 6 monthly reviews. Among the 537 P-IGT who were enrolled in the prevention study, 266 did not receive the SMS intervention (control group) but were reviewed at 6 monthly intervals with OGTT and physical examination for 2 years. They were advised to continue the LSM. This group was included as the P-IGT group for the present analysis. At the end of 5 years they were invited to undergo an OGTT with other biochemical and physical evaluation. This was an observational study. Thirty participants were lost to follow up and 236 were available for the 5th year follow up.

The flow chart (Figure 1) shows the steps in the 5 year assessment of P-IGT and T-IGT.

The study was approved by the Ethics Review Committee of the India Diabetes Research Foundation. All participants gave written informed consent, their physicians were informed of the participation in the follow-up assessment.

Clinical and biochemical assessments at baseline and follow up

Details of lifestyle practices, personal history, medical history including history of diabetes and cardiovascular diseases in first-degree relatives, and use of medication were collected by the research team. Anthropometry including body mass index (BMI) and waist circumference (WC) were measured by standard procedures.[6] Participants with blood pressure readings ≥ 130/85 mmHg were categorized as having hypertension.

World Health Organization (WHO) criteria based on glucose levels in a single 75-g OGTT[7] were used for categorization of glucose tolerance. Individuals were classified as having normoglycemia (NGT) (FPG 5.9 mmol/l; <110 mg/dl, with 2h PG 7.8 mmol/l;<140 mg/dl), prediabetes (IFG: FPG between: >5.9 - < 6.9 mmol/l; 110–125 mg/dl) and/ or IGT with FPG 7.0 mmol/l; <126 mg/dl and 2h PG 7.8– <11.1 mmol/l; 140–199 mg/dl)], and diabetes (FPG 7.0 mmol/l;>126 mg/dl; or 2h PG ≥11.1 mmol/l; ≥200 mg/dl).

Statistical analysis: Continuous variables are presented as mean and standard deviation (for normally distributed variables) or median and inter quartile ranges (IQR) (for skewed variables). Categorical variables are presented as counts and corresponding percentages. Paired and unpaired 't' test were used for comparison of baseline and follow-up values. For comparing the median values, Mann Whitney U test and Wilcoxon Signed Rank Test were used.

Multiple logistic regression analysis (Enter Method) was done to analyze the influence of T-IGT versus P-IGT on the 5 year incidence of diabetes. Independent variables included were family history of diabetes, baseline WC and plasma triglycerides and T-IGT vs P-IGT. The statistical package SPSS, Version 19.0 (IBM statistics, USA) was used.

Table 2: Multiple logistic regression analysis showing variables associated with diabetes

Independent variables	B	Odds ratio	95% Confidence interval		P value
			Upper	Lower	
Positive family history	0.099	1.105	0.771	1.583	0.588
Baseline waist circumference (cm)	0.010	1.010	0.986	1.033	0.424
Baseline plasma triglycerides (mg/dl)	0.001	1.001	0.999	1.583	0.335
T-IGT Vs P-IGT	-1.601	0.202	0.141	0.289	<0.0001

Results

Figure 1 shows the selection of the study groups, design and the final outcome of the study.

Table 1 shows the inter group and intra group comparison of anthropometry and biochemical variables among P-IGT and T-IGT. At baseline, T-IGT had significantly lower values for WC (p=0.042), glucose (P<0.0001) and triglycerides (p=0.045) when compared with P-IGT. At follow up, body weight, BMI and WC increased significantly in the P-IGT whereas among the T-IGT only WC showed a significant increase at the follow up (P<0.0001).

As expected, at follow up the glucose values showed increase in both groups due to presence of diabetes in some participants. Triglycerides increased and HDL-Cholesterol levels improved in both groups.

Figure 2 shows the glycaemic outcomes at the 5th year in the study groups. Among the T-IGT, normoglycaemia was present in a larger number (66.1% in T-IGT Vs 32.2% in P-IGT, p<0.0001) and cases of diabetes were significantly lower (13.7% in T-IGT Vs 44.9% in P-IGT, p<0.0001).

Table 2 shows the results of the multiple logistic regression analysis. The conversion rate to diabetes in 5 years was significantly lower among the T-IGT than among the P-IGT. The OR was 0.202 (95% CI, 0.145-0.296, p<0.0001).

Discussion

This 5 year follow up study, among men showed that the risk of conversion to diabetes was significantly lower among the participants with T-IGT when compared with people with P-IGT. The 5 year risk was 80% less in the T-IGT group.

There are only few long term studies which have assessed the natural history of T-IGT vs P-IGT. The definition of T-IGT has been varied even among those studies which have analyzed the incident rate of diabetes among T-IGT.[8,9] In our study, persons with IGT who showed NGT on a repeat GTT within a week have been termed as T-IGT. In the New Castle Heart Project (NCHP)[8] which followed up European and South Asians with IGT, the term T-IGT has been given if IGT was detected on the first OGTT with a normal repeat OGTT 2-6 weeks later. Persons with P-IGT showed IGT on both OGTTs. The definition used in our study is similar to the above.

In a study in South African Indians the term T-IGT has been used for people who showed NGT on a repeat OGTT at 1 year of follow up.[9] In this 4 year prospective study of 128 subjects with IGT at baseline, it was observed that T-IGT carried no risk of progression to diabetes. In an analysis of the P-IGT subjects in the Indian SMS diabetes prevention study[6] we had noted that the risk of diabetes in 2 years was lower by 75% in persons who reverted to NGT by LSM, during the first 6 months of follow up (HR 0.25).[10] The present analysis shows that T-IGT carries significantly lower risk of diabetes even after a longer period of follow up when compared with people who have P-IGT.

The New Castle Heart Project showed that Europeans were significantly less likely than South Asians to have P-IGT (48 Vs 77%). They also noted that persons with P-IGT had greater BMI, WC and higher fasting and 2 hr post glucose values than those with T-IGT.[8] Similar characteristics were observed in our P-IGT cohort. However, in the above study the conversion rates to diabetes were similar in the South Asians, having either P-IGT or T-IGT (30 Vs 36%) whereas among the Europeans, the conversion rate was higher in P-IGT (29%) than in the T-IGT (13%). The reason for the varied observation in the south Asians in the UK, from that of our population is unclear. The Asian study population in the UK consisted of Indians, Pakistanis and Bangladeshis, whereas our study was done only among Asian Indians.

The small sample size and the absence of women are limitations of the present study. However, the findings from this 5year prospective study are of considerable importance in selecting participants for prevention studies.

Analysis of the earlier Indian Diabetes Prevention Program-1 (IDPP-1), showed that persons with P-IGT had higher levels of BMI, WC and body fat percentage than persons with T-IGT, indicating presence of higher insulin resistance.[11] These findings indicated that P-IGT was associated with higher percentage of indicators of insulin resistance. Present analysis in different cohorts showed similar observations suggestive of higher risk of diabetes among P-IGT than in T-IGT.

A 10 year follow up of population based urban Indian cohort from Chennai reported that among those with NGT (ADA criteria)[12] 19.4% converted to diabetes and 25.7% converted to prediabetes.[13]

Conclusion

In India T-IGT has a low rate of conversion to diabetes which is similar to the rate of conversion occurring among people with NGT. It is significantly lower when compared with those having P-IGT (13.7% Vs 44.9%). Identification of P-IGT will help in selecting persons at a higher risk of diabetes in whom early institution of lifestyle intervention will be needed.

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Author Disclosure Statement

All authors have contributed significantly to the study and the details of their contributions are given below:

Dr. R. Arun: Researched data, Contributed to discussion, Prepared

Manuscript; Dr. A. Nanditha: Contributed to discussion, Reviewed/ edited manuscript; Dr. C. Snehalatha: Researched data, Contributed to discussion, Prepared manuscript; Dr. R. Vinitha: Contributed to discussion, Reviewed/edited manuscript; Ms. Priscilla: Performed the experiments, Helped in data collection; Ms. Mary Simon: Performed the experiments, Helped in data collection; Dr. S. Selvam: Performed the experiments, Helped in data collection, Contributed to discussion; Dr. K. Satheesh: Contributed to discussion, Reviewed/ edited manuscript; Dr. J. Ram: Contributed to discussion, Reviewed/ edited manuscript; Dr. A.P. Naveen Kumar Supported Recruitment and Data collection; Dr. I.F. Godsland: Contributed to discussion, Reviewed/ edited manuscript; Dr. Nick Oliver: Contributed to discussion, Reviewed/ edited manuscript; Dr. D.G. Johnston: Researched data, Contributed to discussion, Reviewed/edited manuscript; Dr. A. Ramachandran: Researched data, Contributed to discussion, Prepared Manuscript.

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