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Original Article

Elevated one hour with normal fasting and 2 h plasma glucose helps to identify those at risk for development of Type2 Diabetes-11 years observational study from south India

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ABSTRACT

Aims: To compare conversion rates of diabetes in subjects with elevated 1 h plasma glucose (1hrPG) during an OGTT with normal glucose tolerance(NGT) subjects over a period of 11 years.
Methods: 4023 subjects were selected from electronic data base of medical records.233 subjects who were followed up for a period of 11 years were included.160 with isolated prediabetes and their combinations were excluded.The remaining 73 were categorized into group1 NGT (n = 37) and group-2 (n = 36) with elevated 1hrPG.Kaplan Meier curves for incident diabetes and Cox proportional hazard model were compared between groups.
Results: During follow up, 10.8% and 44.4% converted to DM in group1 and group2 (p = 0.003). Elevated 1hrPG was associated with incident diabetes(HR 7.9[95%CI 2.2–28.1](p = 0.001)provided better risk assessment.The adjusted risk of event in subjects with elevated 1hrPG is likely to be 7 times more when compared to NGT.Subjects with elevated1hrPG remained free of diabetes for a median period of 7.6 years (95% CI 5.8–7.8) whereas NGT subjects remained free for 10 years (95% CI 8.5–10.0) (p < 0.001).
Conclusion: In conclusion, conversion to DM was higher and risk was 7 times more in subjects with elevated 1hrPG. Elevated 1hrPG during OGTT has to be considered as a distinct entity.

1. Introduction

The worldwide prevalence of diabetes has increased dramatically over the past two decades and the reached epidemic proportions has become a global threat. Oral glucose tolerance test (OGTT) is widely used for identifying individuals with prediabetes or type 2 diabetes. Prediabetes has been defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) based on fasting or 2hr value during a 2 h OGTT [1,2].Individuals in these sub clinical stages such as IGT and IFG are at high risk of developing diabetes and cardio vascular diseases(CVD) [3].Many non diabetic subjects show elevated intermediate glucose response with normal fasting and 2 h value during OGTT. The current recommended diagnostic criteria do not use 1hr plasma glucose (1hrPG) during OGTT to identify those at elevated risk for a diagnosis of type2 diabetes,but a significant number of individuals with elevated 1 h PG progress to type 2 diabetes.

Our previous study showed that the conversion rate to diabetes was similar to IGT in subjects who had a elevated 1hr value during an OGTT. They had higher insulin resistance with normal insulin secretion [4].Subjects with elevated 1 h PG also showed significantly higher prevalence of metabolic syndrome compared to normal subjects [5].Normal subjects with elevated 1hrPG have a worse metabolic profile than those with normal 1hrPG during an OGTT. Defronzo et al. and other workers also showed that glucose value at 1 h (≥155 mg/dl)(≥8.6 mmol/L) during an OGTT is a strong predictor of future risk for type 2 diabetes [6–10].Evidence suggest that the cut point ≥155 mg/dl may identify individuals with reduced β-cell function and this cut point is highly predictive of those likely to progress to diabetes more than HbA_1c or 2 h post load glucose values [6,9,11–13].

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IFG and IGT conditions are well studied for prediction of type 2 diabetes but the clinical implications of using 1hr glucose measurement for prediction of type 2 diabetes are less clear. It is also important to identify these high risk individuals in order to implement preventive strategies. There is a sparse data available on elevated 1 h PG towards risk assessment and its progression towards type 2diabetes.As an extension to our earlier studies in this field we aimed to compare conversion rates of diabetes in subjects with elevated 1 h PG during an OGTT(with a FPG <100 mg/dl(5.6 mmol/L) and 2hr value < 140 mg/dl)(7.8 mmol/L)with normal glucose tolerance subjects(NGT) over a period of 11 years.

2. Subjects, materials and methods

In this observational study, we reviewed electronic database of medical records of a total of 4023 subjects who had undergone an OGTT periodically between the period October 2007–December 2011.

2.1. Inclusion and exclusion criteria

Of the 4023 subjects who underwent baseline OGTT, excluded 1480 subjects who were diagnosed with diabetes during screening.After exclusion of subjects with diabetes,2543 subjects were left. Subjects who lost to follow up OGTT's or with few follow up OGTT's i.e, one to three OGTT's (n = 2310) were further excluded from the analysis. A total of 3790 subjects were excluded and the remaining 233(M:F 155:78) subjects who had follow up OGTT's done once in a year till May 2018 after the baseline OGTT were included in the final analysis(Fig. 1). Demographic details such as age, gender and family history of diabetes were recorded. Anthropometric measurements height and weight were recorded and body mass index(BMI kg/m^2) was calculated. Systolic and Diastolic blood pressure was recorded using mercury sphygmomanometer.The ethics committee of the institution approved the study. Written informed consent was obtained from all the study subjects.

2.2. Biochemical investigations

A fasting venous sample was drawn from all subjects and a standard OGTT was done and plasma glucose was estimated at fasting,1hr and 2hrs after glucose load. Plasma glucose was estimated by glucose oxidase peroxidase method. The fasting serum sample was used for estimation of lipid profile. Glycosylated haemoglobin (HbA_1c %) was measured by HPLC method using Variant turbo Bio Rad equipment (Bio-Rad, Hercules, CA, USA). All the biochemical investigations were done using enzymatic procedures and fully automated biochemistry analyzers. Serum creatinine was assayed with a kinetic test without deproteinization according to the Jaffe method. All the blood samples were collected and estimated in an National Accreditation Board for testing and calibration laboratories (NABL) accredited laboratory.

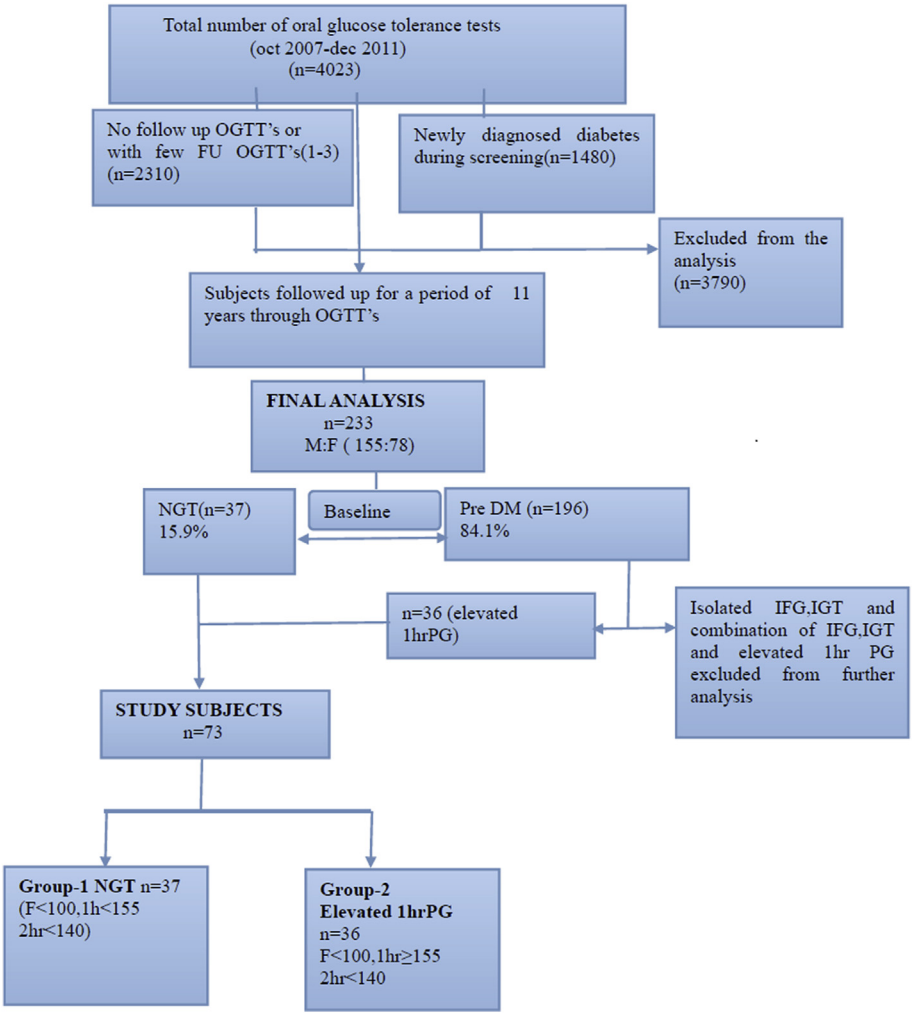

Fig. 1. Shows the flowchart of selection of study subjects from electronic medical records.(FU; Follow up,Pre DM; Prediabetes).

Table 1
Baseline anthropometric and biochemical characteristics of the study groups.

Variables	Group 1 n = 37 (M:F 20:17)	Group 2 n = 36(M:F 30:6)	P value
Age (yrs)	42.6 ± 13.2	48.3 ± 8.4	0.021
BMI (kg/m$^{2)}$	27.5 ± 4	26.9 ± 3.7	0.463
Positive Family history of diabetes n(%)	18 (48.6)	17(47.2)	0.194
BLOOD PRESSURE(mm/Hg)			
Systolic	120.3 ± 12.1	126.4 ± 13	0.039
Diastolic	80.3 ± 7.4	80.6 ± 9.3	0.874
PLASMA GLUCOSE(mg/dl)			
Fasting	91.6 ± 6.7	94.1 ± 4.5	0.069
1 h	126.5 ± 18.5	177.2 ± 19.1	0.001
2 h after oral glucose load	110.1 ± 19	108.2 ± 20.3	0.675
HbA_1c(%)(mmol/mol)	5.6 ± 0.4(37.7)	5.8 ± 0.32(39.9)	0.06
Total cholesterol(mg/dl)	176.7 ± 42.1	187.1 ± 32.8	0.278
Triglycerides(mg/dl)	123.8 ± 47	131.3 ± 45.8	0.522
LDL- cholesterol(mg/dl)	123.8 ± 38.3	117 ± 25	0.473
HDL- cholesterol(mg/dl)	47.6 ± 11.1	45.8 ± 11.3	0.532
Urea (mg/dl)	21.5 ± .5.9	25.6 ± 19.9	0.365
Serum Creatinine(mg/dl)	0.80 ± 0.22	0.75 ± 0.14	0.388

BMI,body mass index; HbA1c,glycosylated haemoglobin; LDL,low density lipoprotein; HDL,High density lipoprotein; SD,standard deviation.
Values are mean ± SD.

2.3. Diagnosis

Diagnosis was made according to the ADA criteria(2). At baseline, 37 subjects had NGT (Group1)[fasting plasma glucose(FPG) value < 100 mg/dl(5.6 mmol/L),1 h value < 155 mg/dl(8.6 mmol/L),2 h < 140 mg/dl (7.8 mmol/L)] and the remaining 196 subjects had prediabetes (IFG, IGT, elevated 1hrPG, combination of IFG,IGT and elevated 1 h PG). IFG was diagnosed if FPG was between 100 mg/dl (5.6 mmol/L) to <126 mg/dl (7 mmol/L) 1 h PG < 155 mg/dl (8.6 mmol/L) and 2 h PG < 140 mg/dl (7.8 mmol/L) and IGT was diagnosed based on FPG <100 mg/dl (5.6 mmol/L), 1hrPG <155 mg/dl (8.6 mmol/L) and 2 h PG between 140 mg/dl(7.8 mmol/L) to<200 mg/dl (11.1 mmol/l). Individuals with elevated 1hrPG had a FPG value of<100 mg/dl, 1hrPG≥155 mg/dl (8.6 mmol/L) and 2hrPG<140 mg/dl (7.8 mmol/L). The 1 h PG cut off value of≥155 mg/dl (8.6 mmol/l)had a sensitivity of 75% and specificity of 79% for predicting future diabetes [6]. Diabetes was diagnosed based on FPG ≥126 mg/dl (7 mmol/L) and/or 2 h PG ≥ 200 mg/dl (11.1 mmol/l). Subjects with IFG,IGT and combinations of IFG,IGT and elevated 1 h PG were excluded from further analysis. NGT subjects (Group1)(n = 37) were compared with subjects with elevated 1hrPG with normal fasting and 2 h value (Group2)(n = 36)(Fig. 1).

2.4. Statistical analysis

Statistical analysis was performed with SPSS statistical software (version 20.0, SPSS,USA). Continuous data were reported as mean ± SD and categorical data as number and percentages. Mean differences between groups were tested by students 't' test and categorical variables were tested by using chi-square test. Cox proportional hazard regression model was derived and compared between the study groups for risk assessment. Hazard ratios (HR) were reported unadjusted and adjusted for age, BMI and family history of diabetes. Kaplan-meier survival curves derived for incident diabetes using log rank test. A P value of <0.05 was considered as statistically significant.

3. Results

At baseline, 37 subjects (15.9%) had NGT (Group1) and 196 subjects(84.1%) had prediabetes. Among 196 subjects with prediabetes, 160 individuals who had isolated IFG, isolated IGT, IFG + IGT, IFG + elevated 1 h PG, IGT + elevated 1 h PG and combination of IFG + IGT + elevated 1 h PG were further excluded from final analysis and included those subjects who had normal fasting and 2 h values but with elevated 1 h PG (n = 36) (Group 2).

The baseline anthropometric and biochemical characteristics of the study groups are shown in Table 1. The group 2 subjects with elevated 1 h PG value were older than group1 subjects (p = 0.021). The body mass index was similar in both the groups. Presence of positive family history of diabetes was also similar in the study groups. Mean systolic blood pressure was significantly higher in group 2 as compared to group 1 subjects. As expected, 1 h plasma glucose value during OGTT was significantly elevated in group 2 than group 1 subjects (p = 0.001) with no significant difference in the fasting and 2 h values between the groups. Mean HbA_1c% was slightly elevated in group 2 and was within the pre-diabetes range. Lipid profile and renal parameters were similar in both the groups.

Table 2 shows the conversion rate of NGT subjects (Group 1) and elevated 1 h PG subjects (Group 2) to diabetes. There was a significant difference between the conversion rate to diabetes among NGT versus elevated 1 h PG subjects(10.8 vs 44.4%) (p = 0.003). 51.3% converted to PreDM in group 1 whereas 50% remained as PreDM in group 2. The percentage of subjects who regressed to NGT was significantly lower in group 2, while 37.8% remained as NGT in group 1.

Fig. 2 shows the results of Cox proportional hazard regression analysis. Elevated 1 h PG was associated with incident diabetes [unadjusted hazard ratio (HR) 8.12 (95% confidence interval CI 2.3–28.0)] [p = 0.001] and provided better risk assessment. The adjusted HR was 7.9 (95%CI 2.2–28.1) [p = 0.001].The adjusted risk of event in subjects with elevated 1 h PG is likely to be 7 times more as compared to NGT subjects.

Fig. 3 shows the results of the Kaplan-Meier survival analysis. The survival curve showed that the median survival time for NGT was 10 years (95% CI 8.5–10.0) and for subjects with elevated 1 h PG it was 7.6 years (95% CI 5.8–7.8) (p < 0.001). The comparison of survival showed that there was a significant difference in the median survival time between the groups. It was noted that the

Table 2
Conversion rate to prediabetes and diabetes in the study groups.

Study groups Baseline	During follow up		
	NGT	Pre DM	New DM*
Group-1 (NGT) 37 (15.9)	14(37.8)	19(51.3)	4(10.8)
Group-2 (Elevated 1hrPG) 36 (15.3)	2(5.5)	18(50)	16(44.4)

Values are n(%).
*P = 0.003(Group1vsGroup2).

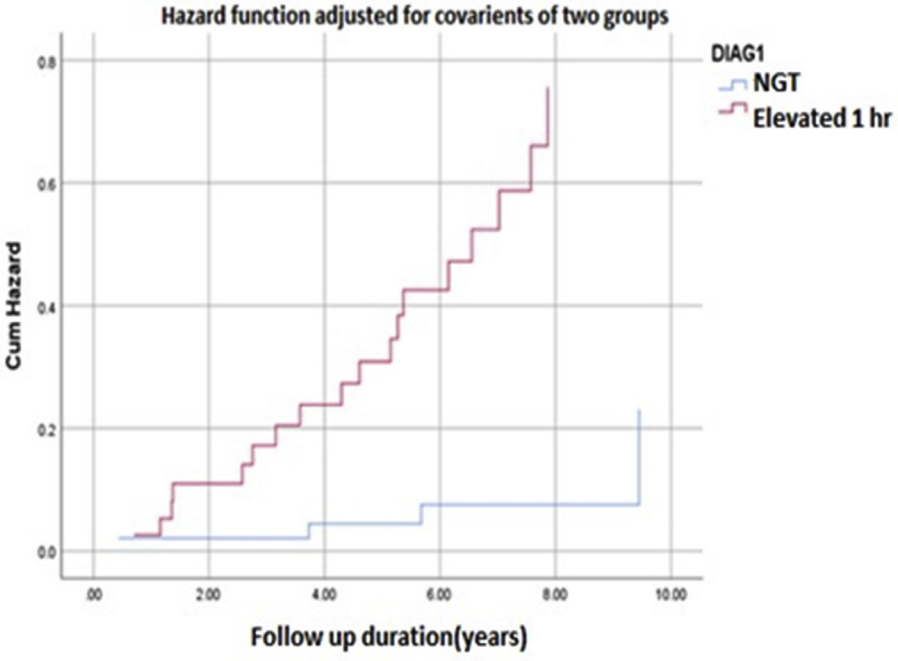

Fig. 2. Shows the results of Cox proportional hazard regression analysis.

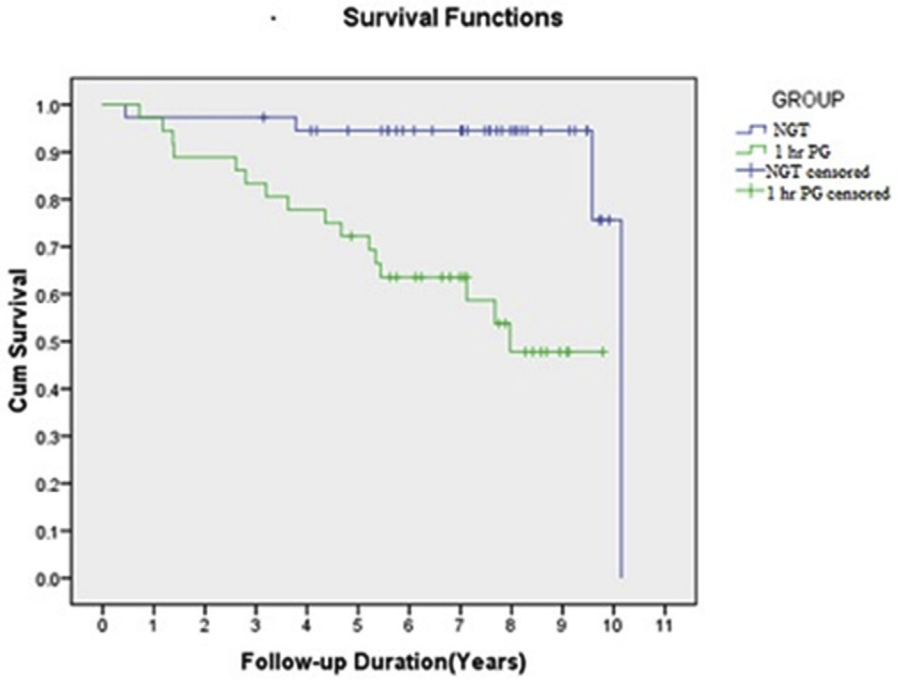

Fig. 3. Shows the results of the Kaplan-Meier survival analysis.

progression was earlier among the subjects with elevated 1 h PG than NGT subjects.

4. Discussion

The current study findings demonstrated that elevated 1 h PG during an OGTT is a significant predictor of future type2 diabetes regardless of fasting and 2hr glucose levels in South Indian Population. Our previous studies highlighted the importance of elevated 1 h PG. The risk was similar to IGT in the development of diabetes and they had metabolic changes [4,5].The current study extends previous findings by comparing risks in groups who had longer follow up duration. The conversion to diabetes was higher in subjects with elevated 1 h PG as compared to NGT subjects. They found to confer higher risk(HR 7.9).The risk of event was likely to be 7 times more among those subjects than NGT subjects. Another study on NGT with 1hr $\geq$ 155 mg/dl and metabolic syndrome found to be at a 5 fold higher risk for type 2 diabetes [6]. Furthermore,in the current study the survival curve showed that the duration free from diabetes was lesser in subjects with elevated 1 h PG than the NGT

subjects. It was 7.6 years for subjects with elevated 1 h PG versus 10 years for NGT subjects. Similar finding was reported from another study from South India [8].The time to development of diabetes was shorter among those with 1 h PG value of ≥155 mg(9.0 ± 0.3 years) (mean ± SE) compared with those with 1 h PG ≥ 143-<155 mg/dl(10.6 ± 0.5 years)and 1 h PG < 143 mg/dl(11.6 ± 0.2 years) [8].

Several studies have previously reported that 1 h PG is a comparable or even better predictor of type 2diabetes than 2hrPG [8,11,12,14].Similarly, in Malmo Preventive Project, a prospective population based cohort study with longer duration of follow up(median follow up 33 years)showed that 1 h glucose is a strong predictor of future type2 DM than 2 h glucose and is associated with diabetes complications and mortality may be due to long exposure to hyperglycemia. These subjects were followed for up to 39 years with registry based recording of events [15]. In a very recent study in US population,1 h PG had a predictive value similar to that of 2 hrPG to assess retinopathy risk. The ability of 1hrPG and 2 h PG to predict the prevalence and incidence of retinopathy was similar. They had suggested that 1 h PG may be considered as an alternative glucose time point during an OGTT [16].Similarly, Bergman et al. highlights the inadequacies of current approaches for diagnosing dysglycemia and proposed that the 1 h post load glucose level during the 75 gms OGTT may serve as a novel biomarker to detect dysglycemia earlier. The author suggested for planning large, prospective multi centre randomized trial with lifestyle intervention in these high risk individuals [17,18].Elevated 1 h PG is associated with subclinical inflammation, lipid disorders and insulin resistance and can be used as a marker for assessing cardiovascular risk too [19].

Our study has few limitations. It is a retrospective analysis of subjects who returned for review to undergo OGTT's periodically. The subjects were not followed up at specified time intervals. It is an hospital based study, the results may not be representative of the general population.The strength of our study was that the subjects had follow up OGTT's for a longer duration. In conclusion, conversion to diabetes was higher in subjects with elevated 1 h PG during an OGTT as compared to NGT subjects. The risk of event was likely to be 7 times more in these subjects than NGT. In the earlier stage of NGT, where the fasting and 2 h PG are normal, it seems that 1 h PG have a useful role in predicting future dysglycemia. Thus, elevated 1 h PG during an OGTT has to be considered as a distinct entity in diagnosis and as a novel approach for early identification of high risk subjects. In addition, there is a need for primary prevention of diabetes among these high risk subjects through lifestyle changes.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.029.

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