Hyperglycemia Exists before the onset of Diabetes: Experience at Prof M Viswanathan Diabetes Research Centre

Dr. Sukanya Nachimuthu, Dr. Vijay Viswanathan

Prof M Viswanathan Diabetes Research Centre, Chennai

Introduction

Non-communicable diseases are the growing public health problem in all socio-economic statuses. A significant contribution is Type 2 diabetes mellitus. According to the Ministry of Health and Family Welfare (MoHFW), Government of India, most of the time, diabetes occurs due to factors like unhealthy lifestyle, diet, adverse physical and social environments (1). The overall prevalence of diabetes in India is 7.3% (from the study conducted in 15 states in India) (2). Prevalence of diabetes is noticed higher in low socio-economic status than the middle and high socioeconomic status. The overall prevalence of pre-diabetes in India is 10.3% (from the study conducted in 15 states in India) (2). In the key findings of the latest version of IDF Atlas 10th edition, 90 million people live with diabetes in the South East Asian region. That is, 1 in 11 adults living with diabetes. This number is expected to reach 113 million by 2030 and 151 million by 2045. Undiagnosed diabetes is another public health problem. In the South East Asian region, over 1 in 2 adults living with diabetes are undiagnosed (3). In the 2019 IDF atlas, 25.2 million people were diagnosed with IGT (Impaired glucose tolerance), and this number is expected to become 32.2 in the year 2030 and 40.7 in 2045. This continuous increase in the prevalence of diabetes and pre-diabetes is a great concern (4).

Hyperglycemia before the onset of type 2 diabetes diagnosis occurs when the individual has higher glucose levels in their blood but lesser than the criteria for diabetes (Table 1). This can be called pre-diabetes (includes the condition called impaired glucose tolerance-IGT and Impaired fasting glucose-IFG).

What is impaired glucose tolerance & impaired fasting glucose?

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) refer to a metabolic state intermediate between normal glucose homeostasis and diabetes (Prediabetes). Higher risk of development of Diabetes.

These two conditions discuss the fasting and 2-hour glucose levels, whereas 1-hour glucose levels also get elevated. In the diagnostic criteria (World Health Organization diagnostic criteria for Diabetes), the 1-hour OGTT normal and abnormal values were not mentioned (Table 1) (5).

What is early glucose intolerance?

Table 1: WHO Diagnostic criteria for Diabetes, IGF, and IGT:

Criteria	World Health Organization	
	FPG	**OGTT 2-hour PG**
Diabetes	≥126 mg/dL (7.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Impaired fasting glucose (IFG)	110 mg/dL to 125mg/dL (6.1 to 6.9mmol/L)	< 140mg/dL (< 7.8mmol/L)
Impaired glucose tolerance (IGT)	< 126 mg/dL (< 7.0 mmol/L)	140mg/dl to 200mg/dl (≥7.8 and < 11.1mmol/L)

Individuals with abnormal intermediate glucose response with normal fasting and two h values during OGTT (Oral Glucose Tolerance Test) are called Early

Glucose Intolerance (EGI). These individuals had higher insulin resistance with normal insulin secretion. The 1-hour OGTT value for EGI will be ≥ 160 mg/dl.

Studies conducted by Prof M Viswanathan Diabetes Research Centre show the importance of identifying early glucose intolerance as a risk factor for the development of diabetes.

A prospective study was conducted in the year 2007, which involves high-risk individuals (6). A program was conducted for the individuals with a positive family history of diabetes on the "prevention of diabetes." A total of 4048 participants were enrolled and followed up in the program. This study only recruited participants who had at least two follow-ups (n = 1659; M: F = 1044: 615). OGTT (Oral glucose tolerance test) was done in all the participants. The study participants were categorized into groups based on WHO criteria as normal glucose tolerance, impaired glucose tolerance, early glucose tolerance groups. The study was repeated to confirm the diagnosis. Newly diagnosed participants with diabetes were excluded from the study.

Age, height, weight, and BMI were recorded. Advice on the prevention of diabetes as improving physical activity and diet was given. Every six months, a reminder for OGTT was sent to the study participants. The study participants were followed up for five years (median). Among the 1659 participants, a subgroup of 418 participants, 118 non-diabetic participants, 68 with IGT, 106 with EGI, and 126 with diabetes were taken for sub-analysis.

Of the total participants, 33.8% had developed diabetes. The mean age and body mass index of EGI and IGT participants were significantly higher than NGT (Normal glucose tolerance) participants. There was a significant difference between the conversion rate among NGTs 99 (21.3%) and EGIs 210 (36.5%) in the total group ($\chi 2 = 27.8$; $p < 0.0001$). The percentage of participants who developed diabetes during follow up was significantly lower in NGT 99 (21.3%) compared to IGT 251 (40.5%) ($\chi 2 = 44.2$; $p < 0.0001$). But there was no significant difference in the conversion rate between the EGIs (36.5%) and IGTs (40.5%) ($\chi 2 = 1.9$; $p = 0.15$). Similar results were observed both in men ($\chi 2 = 2.3$; $p = 0.12$) and women ($\chi 2 = 0.03$; $p = 0.9$).

The risk of diabetes was similar in IGT and EGI versus NGT participants, and no difference ($p > 0.05$) was noted in age (42 ± 9.7 years vs. 42.4 ± 9.8 years), positive family history (21% vs. 18%), and BMI (27.4 ± 4.1 kg/m^2 vs. 27.1 ± 4.1 kg/m^2). EGI participants had the highest BMI when compared with the other groups. By the ROC analysis, a cut–off value of one-hour post glucose of ≥ 160 mg/dl gave a sensitivity of 80% and specificity of 70% to detect abnormal glucose tolerance. The characteristic features of the subgroup showed that the IGT, EGI, and participants with diabetes were older than the participants without diabetes ($p < 0.05$). EGI had significantly higher fasting insulin values than NGT. The 2-hour insulin values were the highest in the IGT, followed by the EGI when compared with NGT and participants with diabetes. HOMA- IR was the highest in DM (Geometric mean 6.6 SD (1.9)), followed by EGI (4.5(2.3)) ($p < 0.0001$ vs NGT, 2.9(2.4)) and IGT (3.9 (2.2)). Early phase insulin secretion denoted by insulinogenic index (ΔI/G) was normal in EGI, NGT, and IGT (NGT - (ΔI/G) is 61(2.0), [Geometric mean (SD)] EGI. 59 (2.1), IGT 58(1.8)). (ΔI/G) in DM (15 (2.4)) was significantly lower in comparison with other groups.

This study has shown that EGI, an intermediary post glucose abnormality, had risks similar to IGT in the development of diabetes. The importance of IFG and IGT has validated the use of fasting and 2 – hour post glucose testing. However, when only these two

tests are performed, participants with EGI are missed out. EGI was noted to be associated with insulin resistance rather than a β - cell defect. EGI participants had higher insulin resistance when compared with normal participants. Lifestyle modifications, including dietary modifications and enhanced physical activity, are likely beneficial in EGI participants, as they have been found to reduce insulin resistance. EGI was found to confer a higher risk for the development of diabetes (OR 2.11) compared with IGT or other risk factors. EGI is an entity that needs to be recognized as a prediabetic condition. This study shows the importance of EGI to be considered as high-risk for the development of diabetes.

Another study from the centre showed the prevalence of metabolic syndrome with elevated intermediate glucose response during an OGTT (7). In this study, the diagnosis of metabolic syndrome was made using ATPIII criteria with modified waist circumference appropriate for Indians.

The analysis revealed that the prevalence of metabolic syndrome was significantly higher in EGI (36.1%) compared to NGT (27.9%) ($x2 = 5.8$, $p = 0.015$). Presence of metabolic syndrome was higher in IGT (57%) when compared with NGT and EGI ($p < 0.0001$). The results of multiple logistic regression analysis with presence of metabolic syndrome as dependent variable showed a significant association with EGI (Odds Ratio (OR) = 1.76; 95% Confidence Interval (CI) 1.23–2.5, $p = 0.001$) and IGT (OR = 3.97, 95% CI 2.7– 5.8, $p = 0.001$). Age ($p = 0.88$) and family history of diabetes ($p = 0.53$) was not significant.

EGI showed a significantly higher prevalence of metabolic syndrome than normoglycemic participants. Both categories of glucose intolerance seem to carry an equal risk for developing diabetes and cardiovascular diseases. Diagnosis of metabolic syndrome among these individuals might help in the prevention of diabetes and cardiovascular disease. Identifying these abnormalities at an early stage in high-risk populations may reduce the burden of diabetes and its complications. A significantly higher prevalence of metabolic syndrome in the EGI group than the normal group was noted.

An 11-year observational study of normal fasting and 2-hour plasma glucose with elevated 1-hour plasma glucose report was conducted to compare the conversion rate of diabetes (8). A total of 4023 participants records were selected from the EMR (Electronic medical records). Participants who were followed up for 11 years (n=233) were shortlisted. In the 233 shortlisted participants, 160 participants were excluded as they had isolated pre-diabetes (and its combinations). The remaining 73 participants were included in the study as two groups: the NGT group (n=37) and the EGI group (n=36). Demographic details of the study participants such as age, gender, and family history of diabetes were recorded. Anthropometric measurements such as height and weight were recorded, and body mass index (BMI kg/m^2) was calculated. Systolic and Diastolic blood pressure was also recorded.

There was a significant difference between the conversion rate to diabetes among NGT versus the EGI group (10.8 vs. 44.4%) ($p = 0.003$). In the NGT group, 51.3% converted to Prediabetes, whereas 50% remained prediabetes in the EGI group. The percentage of participants who regressed to NGT was significantly lower in the EGI group, while 37.8% remained as NGT in the NGT group. Elevated 1-hour plasma glucose 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 an event in participants with elevated 1-hour

plasma glucose is likely to be seven times more as compared to NGT participants. The survival curve showed that the median survival time for NGT was ten years (95% CI 8.5-10.0), and for participants with elevated 1-hour plasma glucose, it was 7.6 years (95% CI 5.8-7.8) ($p < 0.001$). The survival comparison showed a significant difference in the median survival time between the groups. It was noted that progression was earlier among the participants with elevated 1-hour plasma glucose than NGT participants.

Conclusion

Hence, three-point OGTT (Fasting, 1-hour and 2-hour) is important to identify the intermittent elevated glucose levels. This condition is also a significant risk factor for the development of diabetes as IGT and IFG.

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