Can we Change the Natural History of Type 2 Diabetes Mellitus?

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"Not knowing when the dawn will come, I open every door"

–Emily Dickinson

ABSTRACT

In the natural history of type 2 diabetes mellitus (T2DM), there is a stage of prediabetes and a still earlier stage of normal glucose tolerance (NGT). If individuals are identified at these earlier stages, it may be possible to prevent development of T2DM. This is called primordial or primary prevention of diabetes. Once T2DM sets in, attempts should be made to prevent complications and this is called secondary prevention of diabetes. Even after complications set in, we can institute steps to limit disability or provide rehabilitation. This is called tertiary prevention of diabetes. Thus, it is possible to alter the natural history of T2DM at every stage of the disorder.

INTRODUCTION

The number of people with type 2 diabetes mellitus (T2DM) is increasing rapidly and the latest figures are 387 million people with diabetes globally which is projected to rise to 592 million people in 2035. What is worse is that almost half of the people with diabetes remain undiagnosed. The disease burden due to diabetes is higher in low and middle income countries where four out of five people (80%) now reside. India, one of the largest countries in the Southeast Asian region, has more than 67 million people with diabetes, and this is expected to increase to 101 million by 2035. There is thus a need to make efforts to slow down the diabetes epidemic. This article describes how we can try to alter the natural history of T2DM at every stage of the disorder.

NATURAL HISTORY

In the natural history of T2DM, there are various stages like normal glucose tolerance (NGT), prediabetes, clinical diabetes and stage of complications (Fig. 1). Understanding the natural history of T2DM will help to plan effective strategies for prevention of diabetes. Beta-cell dysfunction and insulin resistance (IR) are two major factors responsible for T2DM. Early beta-cell decline is characterized by impairment in the first phase of insulin secretion followed by glucose stimulation, resulting in impaired glucose tolerance and postprandial hyperglycemia. As the disease progresses, the second phase of insulin secretion also declines resulting in fasting hyperglycemia, i.e. impaired fasting glucose or T2DM. We recently showed that even at the stage of prediabetes there is a drastic beta-cell decline (measured by oral disposition index). Evidence from the Pima Indian studies indicate that the pathophysiology underlying the deterioration in glucose tolerance is the same whether from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) or from IGT to T2DM.

In the natural history of T2DM, it is well known that before the stage of prediabetes there is a stage of NGT. Most people tend to treat all subjects with NGT as being completely “normal” with no risk of progression to glucose intolerance. However, it is logical to assume that some individuals with NGT will progress to prediabetes and diabetes. Indeed it has been shown that 40% of individuals, who developed diabetes, had NGT at baseline. There is thus a need to identify these subgroups of NGT subjects who are at increased risk of progression to dysglycemic status. We and others have shown that the 1 hour plasma glucose (HrPG) value during an oral glucose tolerance test (OGTT) could serve to stratify the NGT subjects into different risk groups with respect to the development of prediabetes or diabetes in the future. Thus, it is clear that there is a section of people with the NGT who will progress to glucose intolerance.
Figure 1 clearly shows the stages in the natural history of diabetes and also various stages of prevention of diabetes.

**IDENTIFYING HIGH-RISK INDIVIDUALS**

**Population Based Cohort (CURES)**

Asian Indians have high prevalence of diabetes despite relatively low levels of obesity. There is little data on the incidence rates of diabetes and the rates of conversion through different stages of dysglycemia in the Asian Indian population. We studied the incidence of diabetes and prediabetes and determined the predictors of progression in a population-based Asian Indian cohort. A total of 3,589 individuals from the Chennai Urban Rural Epidemiology Study (CURES) were followed up for a median of 8.9 years (22,905 person years follow-up). In this cohort, among those with NGT, 19.4% converted to diabetes and 25.7% to prediabetes, giving an overall conversion rate to dysglycemia (diabetes + prediabetes) of 45.1%. Among those with prediabetes, 58.9% converted to diabetes. Predictors of progression to dysglycemia were advancing age, family history of diabetes, waist circumference, physical inactivity, 2-hour plasma glucose, HbA1c and low high-density lipoprotein (HDL) cholesterol. From the same cohort, for the first time, the relative contributions of various modifiable risk factors, singly and in combination were studied to look at the population attributable risk (PAR) in Asian Indians. This study reported that more than 80% of incident diabetes cases could be prevented by modifying five easily identifiable risk factors: i.e. obesity, physical inactivity, diet, hypertriglyceridemia and low HDL cholesterol. About 51.7% could be prevented just by modifying diet and by increasing physical activity and this figure increased to 70.8%, if abdominal obesity was also corrected. Thus, all efforts should be made to encourage healthy diets and increasing physical activity in our country.

**Clinic Cohort**

From the clinic cohort of patients seen at our center at Chennai, we looked at the predictive value of 1HrPG concentrations in predicting progression to T2DM among Asian Indians with NGT. We reviewed the records of 32,809 individuals who had undergone an OGTT in the period 1997–2010. All individuals with a baseline fasting plasma glucose (FPG) value of less than 100 mg/dL and a 2HrPG load value of less than 140 mg/dL with a minimum of one follow-up OGTT done at least a year later were included in the study (n = 1,179). During this 13 year follow-up, 392/1,179
NGT subjects (33.2%) developed prediabetes and 148/1,179 NGT subjects (12.6%) developed T2DM. The estimated time for the development of diabetes and prediabetes (presented as mean ± SE) was significantly shorter with those with 1HrPG values more than or equal to 155 mg/dL converting to diabetes in 9.0 ± 0.3 years compared with 10.6 ± 0.5 years for those with 1HrPG of more than or equal to 143 to less than 155 mg/dL and 11.6 ± 0.2 years (p < 0.001) for those with 1HrPG less than or equal to 143 mg/dL. Time for conversion to prediabetes was 5.6 ± 0.2 years for 1HrPG values more than or equal to 155 mg/dL, 6.7 ± 0.4 years for 1HrPG more than or equal to 143 to less than 155 mg/dL, and 8.7 ± 0.3 years for 1HrPG of less than 143 mg/dL (p < 0.001).

Receiver operating curves (ROCs) were also constructed to see the 1H cut points which predicted prediabetes and diabetes respectively. The ROCs revealed that for predicting future prediabetes a baseline 1HrPG of 143 mg/dL and for future diabetes a baseline 1HrPG of 155 mg/dL were useful cut points. Our study thus shows that doing a 1H glucose estimation during an OGTT, may be useful as this helps to identify those likely to progress to prediabetes or diabetes in the future.

Walker et al. demonstrated that in a cohort of non-diabetic subjects, over a 5-year period, glucose tolerance deteriorated at a rate of 1.4% per year for individuals with no family history of diabetes and 4.0% per year for subjects who had a first-degree relative with diabetes. This underlines the increased risk of progression in those NGT subjects with a positive family history of T2DM. Hence, it is clear that in order to prevent diabetes, steps to be taken to identify those in the prediabetic range so that we can prevent diabetes.

**INSULIN SECRETION AND SENSITIVITY AMONG INDIVIDUALS AT RISK**

Lower insulin sensitivity levels are mandatory for any newly diagnosed diabetes. Studies on the association between insulin sensitivity and development of impaired glucose tolerance are limited. The reduction in insulin sensitivity among IGT subjects is similar to those who have NGT but much lesser than incident diabetes cases. The role of insulin secretion and beta-cell function as predictors of T2DM is unclear. Alterations in insulin secretion might be associated with an increased risk of T2DM. Again, even mild changes in whole body insulin sensitivity at young age, is a precursor of hyperglycemia of any severity [ranging from impaired fasting glucose (IFG) to overt diabetes]. When beta-cell glucose insensitivity is measured, it is shown to be a powerful determinant of glucose tolerance and an accurate predictor of its changes over time regardless of the actual amounts of insulin secreted.

Among the NGT individuals, beta-cell dysfunction and consequent hyperglycemia occurred without any concomitant reduction in insulin sensitivity.

**ARE BETA-CELL FUNCTION AND INSULIN SENSITIVITY ALTERED IN NGT SUBJECTS WITH ELEVATED ONE HOUR PLASMA GLUCOSE (1HrPG)?**

We had earlier shown that in Asian Indians both insulin secretory defects and IR are progressively worse in subjects with prediabetes and diabetes. In our clinic cohort, we showed that NGT subjects with elevated 1HrPG values are characterized by both significantly lower beta-cell dysfunction and insulin sensitivity. However, these impairments are better captured by OGTT indices that incorporate post-glucose-load, i.e. 30 minutes or 2-Hour OGTT indices rather than by the fasting (0’) indices. If preventive measures can be adopted in this subset of NGT by diet, exercise and weight reduction, it could make diabetes prevention more cost effective.

Recently a study assessed the relevance of OGTT in predicting T2DM and reported that 1HrPG is a valuable prediction tool for identifying adults at risk for future T2DM. 1HrPG is simpler, faster and cheaper to collect than the area under the curve (AUC) glucose values as only one measurement is needed for 1HrPG whereas four to five are needed in the case of AUC glucose values. Thus, 1HrPG provides better prediction and saves money and time in the clinical and also in epidemiological set up, but also provides comfort for individuals who undergo the test. Also, the 1HrPG outperformed the prediction model of multiple clinical risk factors like age, gender, BMI and family history of T2DM.

One study demonstrated that a correlation between post-load hyperglycemia in NGT and nonalcoholic fatty liver disease (NAFLD). It is also observed that 1HrPG elevated NGT individuals (OGTT glucose ≥ 155 mg/dL) potentially not only have an increased risk of T2DM, additionally if liver ultrasound was performed they are also at risk for NAFLD. If both these parameters are identified in them, it could easily target individuals for more effective diabetes prevention programs and also to delay any further adverse clinical outcomes.

Another study suggests that prevention would be more effective if it is done prior to developing the prediabetes stage. More studies are needed to identify people at risk to study the disease development among them.

**MODIFYING CLINICAL PRACTICE**

First, screening to identify early diabetes and prediabetes should become routine. Currently the ADA recommends screening with OGTTs or measurement of fasting plasma glucose or hemoglobin A1c.
STRATEGIES FOR PREVENTION AND MANAGEMENT

From the current scenario of diabetes in India, it is clear that prevention of diabetes and its complications is the urgent need of the hour. Prevention of diabetes can be done at every stage in the natural history of diabetes resulting in four levels of diabetes prevention. Primordial and primary prevention contribute most to the health of the whole population by preventing the onset of the disease and its risk factors, while secondary and tertiary prevention are focused on restoring the health of individuals with disease or providing rehabilitation.

At the Stage of NGT

If preventive measures can be adopted in high risk NGT individuals by diet, exercise and weight reduction, it could make diabetes prevention more cost effective by reducing the risk factors for diabetes like obesity. This is called “Primordial Prevention” (by individual or mass media education programs).

At the Stage of Prediabetes

We can prevent progression to clinical diabetes. This is called “Primary Prevention” (through lifestyle or drug interventions).

At the Stage of Clinical Diabetes

We can prevent progression to stage of complications. This is called “Secondary Prevention” (by good control of blood sugar, blood pressure and lipids).

Stage of Complications

This stage, we can still try to prevent the disease from going to the end stage of complications. This is called “Tertiary Prevention” (by limiting disability and initiating rehabilitation measures).

CONCLUSION

Not all individuals with NGT individuals are truly “normal”. Some of them may progress to glucose intolerance while others belong to “nonprogressors” group. To identify these “high risk” individuals who are likely to progress, a three sample OGTT, i.e. Fasting 1 hour and 2 hour should be done routinely. Those with elevated 1 hour value are a high-risk group who could be subjected to preventive therapies such as diet, exercise and weight reduction. This could make diabetes prevention more cost effective. However, we should try to address at all stages of the natural history of T2DM and offer appropriate prevention strategies at each stage of the disorder.

REFERENCES


