Pre-diabetes denotes a stage prior to clinical onset of diabetes. This includes two conditions namely Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG). Over one third of subjects with pre-diabetes develop diabetes within five years. Individuals with pre-diabetes are not only at high risk for developing diabetes but are also considered to be at increased risk for coronary artery disease.

Although lifestyle modification i.e diet, physical activity and weight loss have been clearly shown to prevent diabetes in people with pre-diabetes in several large studies like the Diabetes Prevention Program [DPP] and Diabetes Prevention Study [DPS], additional strategies for high-risk individuals are urgently needed. Moreover application of these trials to real life is very difficult as people are not always willing for lifestyle modification. In this context, the recent Diabetes REduction Assessment with ramipril and rosiglitazone Medication [DREAM] trial results have great implications, particularly in Indians owing to the high risk for diabetes and cardiovascular disease.

**DREAM [Diabetes Reduction Assessment with ramipril and rosiglitazone Medication] Trial**

The DREAM study was based on earlier evidence that thiazolidinediones (TZD) and Angiotensin Converting Enzyme Inhibitor (ACE-I) prevent diabetes. Ramipril, an ACE-I was shown to prevent cardiovascular events in high-risk people, including those with diabetes, in the Heart Outcomes Prevention Evaluation (HOPE) study. Secondary findings indicated that ramipril may also prevent diabetes. The Troglitazone in Prevention of Diabetes [TRIPOD] study showed that troglitazone, the first TZD introduced in the market could prevent diabetes. Unfortunately this study was terminated as troglitazone was withdrawn from the market due to liver toxicity. Rosiglitazone is another TZD currently used to treat diabetes. Rosiglitazone activates peroxisome proliferator-activated gamma receptors and increases peripheral insulin sensitivity and thus decreases insulin resistance.

The aim of the DREAM study was to determine the effect of ramipril and rosiglitazone in preventing diabetes in subjects with pre-diabetes [IGT or IFG]. The study had four arms and the study participants were provided with either or both the drugs or a placebo. DREAM study recruited 5,269 people with pre-diabetes from 191 clinics in 21 countries world-wide. McMaster University, Hamilton, Ontario, Canada was the coordinating centre for the study. Six Indian centres participated and contributed over 650 pre-diabetic individuals to the trial. Results of the trial were recently presented at the 42nd Annual Meeting of the European Association for the Study of Diabetes at Copenhagen and published online in the Lancet [Rosiglitazone arm] and the New England Journal of Medicine [Ramipril arm].

**Beneficial effects of rosiglitazone in preventing diabetes**

Of the 2635 study subjects taking rosiglitazone, 280 [10.6%] developed diabetes compared to 658 out of 2634 [25.0%] in the placebo arm. The hazard ratio [HR] for developing diabetes was 0.38 [95% confidence interval: CI] [0.33 - 0.44] which mean diabetes was prevented by 62%. Additionally, rosialitazone promotes regression to normoglycemia by 70% compared to placebo. Though death rates were not significantly different in both the study groups, it was slightly lower in the rosiglitazone arm. Overall, 8 mg of rosiglitazone daily along with lifestyle recommendations decreased the occurrence of primary end-points which includes diabetes or death by 60%.

An interesting observation in the study was that the diabetes risk reduction increased in those with greater body weight. In other words, obese subjects benefited the most. The hazard reduction for diabetes or death was 40% in people with body mass index <28 kg/m², which increased to 68% in subjects with body mass index: >32 kg/m². Similar results were observed with regard to abdominal obesity defined based on waist circumference. Despite increase in body weight and body mass index, there was a significant decrease in waist to hip ratio indicating redistribution of fat from the more harmful central (abdominal) areas to the peripheral areas (hip). The effect of rosiglitazone on the primary endpoints was beneficial irrespective of age, sex or ethnic group. Though there was no significant difference in the overall cardiovascular events between study groups, the frequency of non-fatal heart failure was higher in the rosiglitazone arm compared to the placebo group. However, there were no serious episodes of cardiac
failure in the trial. Yet another interesting observation in the study was that rosiglitazone decreased serum ALT levels, indicating that it is hepato-friendly, in contrast to troglitazone.8

The diabetes prevention effect of rosiglitazone may be due to its insulin sensitizing effect.13 However, it could also be a glucose masking effect. After the wash-out period, the sustainability of the effect of rosiglitazone needs to be assessed further.

Effect of ramipril on prevention of diabetes and regression to normal

In contrast to rosiglitazone, ramipril did not prevent diabetes, as nearly 17.1% of participants on ramipril and 18.5% on placebo developed diabetes. However, regression to normal in the ramipril arm was significantly higher compared to the placebo arm [42.5% vs 38.2%], HR:1.16 [95% CI:1.07-1.27]. As expected, blood pressure decreased significantly in the ramipril arm compared to placebo. Median levels of two hour post-load plasma glucose levels, but not fasting plasma glucose levels was significantly lower in the ramipril compared to placebo [135.1 mg/dl vs 140.5 mg/dl, p=0.01]. There was no difference in the cardiovascular end points between the study arms.9

A metaanalysis on 12 trials using ACEIs revealed that ACEIs had a beneficial effect in preventing diabetes.13,14 The DREAM study results are however, not in agreement with this observation. This discrepancy could be due to the following reasons: 1. earlier trials were not designed to assess prevention of diabetes as the primary endpoint unlike DREAM, leading to a possibility of ascertainment bias; 2. unlike earlier trials, DREAM recruited study subjects with pre-diabetes and not subjects with high risk for cardiovascular disease like hypertension or diabetes; 3. follow-up required for ramipril to exert its effect may be longer than the study duration of DREAM which was only three years. Hence there is a possibility that if the study was extended, ramipril could have had a modest beneficial effect in preventing diabetes.

In summary, the DREAM study very clearly demonstrates that rosiglitazone which is already used in treatment of diabetes, may significantly reduce the chances of developing the disease when taken by those at high risk such as those with pre diabetes. As pre-diabetic subjects have an increased risk for cardiovascular events, if we can prevent diabetes, the occurrence of serious complications such as cardiovascular disease and microvascular complications of diabetes could also possibly be prevented.

How do the study results impact India?

Recent studies within the Indian subcontinent show that in urban India, prevalence rates of diabetes are fast approaching those seen in more affluent migrant Indians.15,16 The Chennai Urban Rural Epidemiology Study [CURES] conducted on a representative population of Chennai indicated a rising trend in prevalence of diabetes. The overall crude prevalence of diabetes in CURES is 15.5% [age standardized: 14.3%] which includes 6.1% self-reported diabetes and 9.4% previously undiagnosed diabetes. The prevalence of diabetes in Chennai city increased by 39.8% from 1989 to 1995 [8.3% to 11.6%], by 16.3% in the next five years [11.6% to 13.5%], and by 6.0% in the subsequent four years [13.5% to 14.3%]. Thus, within a span of 15 years, the prevalence of diabetes in Chennai increased by 72.3%.17 It is likely that similar increases occur in other urban areas also.

Prevalence of IGT in the CURES study was 10.2%. The age-standardized prevalence of IGT increased by 9.6% from 1989 to 1995 [8.3% to 9.1%] and by 84.6% between 1995 and 2000 [9.1% to 16.8%]. However, it decreased by 39.3% between 2000 to 2004.17 The decrease in prevalence of IGT is of importance as this could reflect rapid progression from normal through IGT to diabetes, leading to drastic increase in prevalence of diabetes due to a worsening diabetogenic environment. These observations clearly emphasize the need for preventative measures to reduce the health burden due to diabetes. It is very likely that a similar scenario exists for other parts of India although no secular trends are available.

The PODIS study18 showed that 5.2% of adults aged ≥ 20 had pre-diabetes in India which translates to approximately 30 million individuals with pre diabetes. If no intervention is done, in five years, the number of pre-diabetic adults who will get converted to diabetes would be approximately 10 million. This will substantially increase the number of people with diabetes in India. If we add pharmacotherapy viz. rosiglitazone to lifestyle recommendations, nearly 5 million people will be prevented from developing diabetes.

So should we start prescribing drugs to prevent diabetes and cardiovascular disease in pre-diabetic individuals? Obviously lifestyle modification still remains the first step as it is the healthiest and most cost-effective intervention measure. However, if this does not work, or for very high risk subjects, pharmacotherapy using rosiglitazone may be an option. While ramipril cannot be recommended for prevention of diabetes, the fact that it lowers plasma glucose levels favourably and its cardiovascular benefits encourages advising the drug for pre-diabetic subjects with hypertension, microalbuminuria or high cardiovascular risk.

There are still several unanswered questions: will rosiglitazone be able to sustain its effect if the drug is withdrawn? What will be the cost effectiveness of using rosiglitazone for prolonged periods of time? Future studies need to address these issues.
*Dr. V Mohan is a member of the Steering Committee of DREAM and a member of the Writing Committee for the Lancet paper.

REFERENCES


