Selected Summaries

Reducing the risk of development of diabetes: Do we have an answer?

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SUMMARY

This article reports on the Diabetes Prevention Program Outcomes Study (DPPOS) which is an observational follow-up study of the Diabetes Prevention Program (DPP). The DPPOS aimed at comparing the risk of incident diabetes among those individuals who achieved normal glucose tolerance during the course of the DPP to that of those who had persistent pre-diabetes.

Of the 3234 DPP participants eligible to participate in the DPPOS, 2761 individuals participated (85%), following a 13-month bridge period between the end of the DPP and the beginning of the DPPOS. These 2761 individuals (909 formerly assigned to the lifestyle arm, 921 assigned to metformin and 931 assigned to placebo) were followed up for a median of 5.7 years (mean 5.4 years, range 0.01–5.98 years). Seventy-two per cent of the 2761 participants (*n*=1990; 736 originally randomized to lifestyle modification, 647 to metformin, 607 to placebo) had either persistent pre-diabetes or regressed to normal glucose tolerance during the course of the DPP and were included in the analysis. The remaining 771 subjects had progressed to diabetes and were excluded from the analysis. Assessment of outcomes was done at 6 and 12 months, as during the DPP. The primary outcome was the development of diabetes. Diabetes, pre-diabetes and normal glucose tolerance were defined using the American Diabetes Association (ADA) criteria.

The study showed that participants who achieved normal glucose tolerance at least once during the DPP had a 56% reduced risk of developing diabetes during the DPPOS. The risk reduction was strongly related to the number of times normal glucose tolerance was achieved. Those who achieved normal glucose tolerance once had a 47% risk reduction, those who achieved it twice had a risk reduction of 61% and those who achieved normal glucose tolerance three times during the DPP the risk reduction was 67%. This risk reduction was independent of randomization into lifestyle, metformin or placebo arms during the DPP. The study also showed that age of <45 years and African American ethnic origin were associated with increased risk of diabetes while female gender was associated with an increased chance of regression to normal glucose tolerance.

The participants who achieved normal glucose tolerance had a higher beta cell function and insulin sensitivity, lower waist circumference and greater weight loss compared to those with persistent pre-diabetes. Surprisingly, increased weight loss during the DPP adversely affected diabetes risk during the DPPOS (HR 1.2 [1.15–1.39], p<0.0001) independent of previous treatment. Those who consistently had pre-diabetes during the DPP despite intensive lifestyle intervention had an increased risk of diabetes during the DPPOS (HR 1.31 [1.03–1.68], p=0.03).

The authors conclude that for someone with pre-diabetes, early intervention to restore normal glucose tolerance, however transiently, is important to reduce the risk of development of diabetes in the future. The strategy to achieve this is unimportant as long as the end-result of normal glucose tolerance is reached.

COMMENT

It is estimated that there are currently 366 million individuals with diabetes worldwide and this is projected to increase to 552 million by the year 2030.[1] In India, there were an estimated 62.4 million individuals with diabetes as of 2011.[2] This is expected to increase to 101 million by the year 2030.[1] The epidemic of diabetes has far-reaching implications on the health and socioeconomic well-being of not only individuals, but also entire nations. Prevention of diabetes is therefore the need of the hour.

'Intermediate hyperglycaemia' or 'pre-diabetes' refers to a state in which individuals have blood glucose values below the diagnostic thresholds for diabetes, but above the currently accepted 'normal' values. Individuals with pre-diabetes are known to have an increased risk of progression to diabetes; indeed, if left untreated, around 11% of these individuals progress to diabetes every year.[3] Furthermore, individuals with pre-diabetes have also been shown to have an increased risk of developing diabetic macro- and microvascular complications, albeit not to the extent seen in individuals with diabetes.[4] Since the early 1990s, several large trials have looked at the feasibility of preventing the development of diabetes in these high-risk individuals, using intensive lifestyle modification, medications, or a combination of the two.[3,5–7] From these trials, lifestyle modification, and to a lesser extent, metformin, have been found to have the greatest effect on retarding the progression of pre-diabetes to diabetes.

The DPP, one of the landmark trials alluded to above, showed that lifestyle intervention results in the most significant risk reduction for development of diabetes (58% for lifestyle intervention versus 31% for metformin).[3] The present DPPOS has assessed the DPP participants from a rather different perspective. Instead of looking at intervention strategies, the focus was on the outcome measure (values of blood glucose). Although participants were followed up based on the original randomization of the DPP, they were divided into those with persistent pre-diabetes and those who reached normal glucose tolerance. The results clearly show that individuals who achieved normal glucose tolerance even once during the 3.2 year study period of the DPP had a lower risk of developing diabetes during the 5.7 year period of the DPPOS, irrespective of the arm to which they had originally been randomized.

This brings out a new perspective for clinicians wherein the focus for patients with pre-diabetes should be on attainment and maintenance of normoglycaemia. All too often, clinicians are content to allow patients with pre-diabetes to persist in that state, without actively trying for attainment of normoglycaemia. The

results of this study show that a more active approach might be worthwhile in these individuals in that it might reduce the long-term risk of diabetes. This, along with the small but definite risk of complications of diabetes associated with the pre-diabetic state, makes the attainment of normoglycaemia a desirable aim. For those individuals who fail to achieve normoglycaemia even with intensive lifestyle changes and the use of metformin, more intensive treatment might be needed for long-term reduction in the risk of diabetes. What exactly such intensive treatment should entail remains to be elucidated by further studies.

India has more than 77 million people with pre-diabetes.[2] Efforts to prevent these individuals from developing diabetes therefore assume importance if the epidemic of diabetes is to be arrested. In addition, this study also shows that pre-diabetes occurring in younger age groups has an increased risk of conversion to diabetes. Whether this is because of the longer duration of the pre-diabetic state (due to the earlier age of onset) or whether the phenomenon of anticipation confers a more aggressive type of disease, is a matter of speculation. Irrespective of the reason, it is of specific importance to us in India because of the earlier age of onset of both diabetes and pre-diabetes.[2]

In conclusion, the DPPOS provides a case for more intensive treatment of individuals with pre-diabetes. However, the following questions remain:

1. For individuals who continue to have pre-diabetes in spite of lifestyle modification and metformin treatment, what should be the next line of management?
2. Does regression to normoglycaemia also decrease the risk of complications of diabetes which are known to occur as a continuum and are present even in individuals with pre-diabetes?
3. To what extent to do these conclusions apply to Asian Indians?

Further studies are needed to answer these questions.

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Continuous positive airway pressure for metabolic syndrome in obstructive sleep apnoea

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CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011;**365:**2277–86.

SUMMARY

The cardiovascular implications of metabolic syndrome, a condition characterized by a constellation of metabolic disorders including abdominal obesity, insulin resistance/glucose intolerance and atherogenic dyslipidaemia, are being increasingly understood in recent years. The intriguing relationship between metabolic syndrome and obstructive sleep apnoea (OSA) and consequences of metabolic syndrome in patients with OSA is presently the subject of extensive research. This prospective, double-blind, placebo-controlled, cross-over study conducted at the All India Institute of Medical Sciences, New Delhi investigated whether treatment with continuous positive airway pressure (CPAP) would modify the components of metabolic syndrome patients with OSA syndrome (OSAS) that was of moderate or greater severity, defined as an apnoea–hypopnoea index (AHI) score of ≥15 with excessive daytime somnolence.

Patients with OSAS were randomly assigned to undergo 3 months of therapeutic CPAP followed by 3 months of sham CPAP, or *vice versa*, with a washout period of 1 month in between. Before and after each intervention, measurements of anthropometric variables, blood pressure, fasting blood glucose levels, insulin resistance, fasting blood lipid profile, glycated haemoglobin levels, carotid intima–media thickness (CIMT) and visceral fat were obtained. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, applying Asian cut-off values for abdominal obesity. Seventy-five of the 86 patients (87%) had metabolic syndrome at the time of recruitment (38 in the CPAP-first group and 37 in the sham-first group). In comparison with sham CPAP, CPAP treatment was associated with significant mean decreases in systolic blood pressure (3.9 mmHg, 95% CI 1.4–6.4, p=0.001), diastolic blood pressure (2.5 mmHg, 95% CI 0.9–4.1, p<0.001), serum total cholesterol (13.3 mg/dl, 95% CI 5.3–21.3, p=0.005), non-high-density lipoprotein cholesterol (13.3 mg/dl; 95% CI 4.0–21.8, p=0.009), low-density lipoprotein cholesterol (9.6 mg/dl, 95% CI 2.5–16.7, p=0.008), triglycerides (18.7 mg/dl, 95% CI 4.3–41.6, p=0.02), and glycated haemoglobin (0.2%, 95% CI 0.1–0.4, p=0.003).