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. 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.

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

Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadirhavanan T, Lakshmy R, Jagia P, Kumar A. (Departments of Medicine, Biostatistics, Cardiac Biochemistry, Cardiac Radiology and Radiodiagnosis, All India Institute of Medical Sciences, New Delhi; and the Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.) CPAP for the metabolic syndrome in patients with obstructive sleep apnoea. 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, glycaemic 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=0.002), and glycaemic haemoglobin (0.2%, 95% CI 0.1–0.4, p=0.003).
The results of this study suggest that in patients with moderate-to-severe OSAS, 3 months of CPAP therapy lowered blood pressure and partially reversed the metabolic abnormalities.

COMMENT

Considered by many as God’s gift to the human race, sleep has intrigued scientists for several generations. Sleep medicine is a relatively young discipline and is an emerging specialty in India. Prevalence of OSAS in studies from the West has ranged from 0.3% to 5%, affecting 2%–4% of middle-aged men and 1%–2% of middle-aged women; the majority of affected individuals remain undiagnosed.14 Even though sparse epidemiological data are available from India on the epidemiology of OSA, a well-conducted, two-stage, cross-sectional community-based prevalence study with a large sample size from Delhi5 showed the overall prevalence of OSA and OSAS to be 13.7% and 3.8%, respectively. If these figures are extrapolated to India’s population, it is estimated that 13.7% of the population has OSAS, and therefore, CPAP remains the most effective treatment for moderate-to-severe OSA. CPAP as a form of treatment is also low cost and reduces the number of emergencies. However, CPAP treatment has not been widely adopted due to patient non-compliance, which is higher in India. The prevalence of metabolic syndrome has been higher in patients with OSA as compared to non-OSA patients.7 The co-occurrence of metabolic syndrome and OSA has been termed as ‘syndrome Z’.8 In a community-based study from Delhi, the estimated population prevalence of syndrome Z in subjects aged 30–65 years was 4.5% (95% CI 3.7–5.3%).9 Among subjects referred to a sleep laboratory for polysomnography (n=227), the prevalence of syndrome Z (65%) was much higher,10

In addition to correction of modifiable risk factors such as recent weight gain, alcohol, sedative/hypnotic use, cigarette smoking, and chronic nasal obstruction, and appropriate treatment of associated comorbid conditions such as systemic hypertension, atherosclerotic disease, heart failure, hypothyroidism and chronic lung disease among others, CPAP remains the most effective therapy for symptomatic patients with OSAS.11 CPAP eliminates upper airway flow limitation by acting as a mechanical stent of the upper airway, stabilizing the upper airway, augmenting the upper airway dilator muscle tone.

The effect of CPAP on the components of metabolic syndrome is not yet fully understood. Barring a few exceptions,12 most studies13–18 have documented a decrease in blood pressure with the use of CPAP. Studies on the effect of CPAP on insulin resistance15,16,17 and lipid profile11,18–20 have yielded conflicting results. The effect of CPAP on metabolic syndrome in patients with OSA was divergent in two studies.13,21 However, most of the studies on CPAP assessing the effect of this intervention on the components of metabolic syndrome have been hampered by small sample size, a short duration of intervention, and the absence of a control group or a washout period.12,13,16,17,21

An earlier randomized cross-over trial11 did not show a significant reduction in the prevalence of metabolic syndrome after 6 weeks of CPAP therapy. However, this study observed that 20% of patients, metabolic syndrome resolved within 3 months. Similar results were noted in an uncontrolled trial22 where a significant decline in the prevalence of metabolic syndrome was documented after 6 months. In this study, a significant reduction in blood pressure was documented with the use of CPAP. Furthermore, there was also a significant improvement in the ratio of high density lipoprotein (HDL) to total cholesterol and levels of total cholesterol, triglycerides, and low density lipoprotein (LDL) and non-HDL cholesterol with CPAP treatment. As seen in some other studies,13,18,20,21 a significant increase in HDL cholesterol was evident only in patients who were compliant to CPAP treatment. Similarly, improvement in CIMT was also evident only in compliant patients. While several uncontrolled studies reported a decrease in insulin resistance,16,17 this study showed no effect on fasting blood glucose, fasting insulin or insulin resistance with CPAP. In an earlier publication by the same group,18 contrary to the independent relationship reported in Chinese patients,23 it was observed that insulin resistance in Indian patients is dependent on obesity rather than OSA. Possible racial or ethnic differences among the study populations may have contributed to these differences. Even though CPAP did not result in a significant change in abdominal circumference, a significant decrease in body mass index (BMI) and abdominal fat could be demonstrated. Whether this was due to the direct effect of CPAP therapy as a result of its effects on leptin levels or a consequence of increased physical activity, the beneficial effect appears to be significant.

This study is a well-conducted, placebo-controlled, double-blind, randomized, cross-over study with a large sample size and a long follow-up. The adequacy of the 1-month washout period chosen is questionable. However, in the absence of clear guidelines on the same, and considering issues such as ensuring patient safety and preventing drop-outs, one month seems to be a reasonable washout period. Despite adequate care taken in blinding and random treatment allocation, patients in the two intervention groups differed at baseline with regard to key characteristics such as total cholesterol, triglyceride and glycated haemoglobin values. These differences are unlikely to have influenced the results as this was a cross-over trial. However, ambulatory blood pressure measurements and repeat polysomnographic examination were not done in this study.

Even giving allowance to issues central to a cross-over study design,24–27 such as the carry-over effect of CPAP treatment and the non-applicability of intention-to-treat analysis, the tangible benefits documented appear to have far-reaching consequences. The reduction in systolic blood pressure of 3.8 mmHg and diastolic blood pressure of 2.4 mmHg, along with a decrease in LDL cholesterol level of 9.8 mg/dl after CPAP therapy, suggest a significant clinical benefit that is likely to result in a significant cardiovascular risk reduction. The effect of CPAP therapy in deducing BMI and visceral fat needs to be studied further in different races and ethnic groups.

The results of this study also stress the need for a bi-directional screening for OSA and metabolic syndrome, i.e. actively detecting metabolic syndrome in patients with OSA and vice versa. In India, CPAP machines are expensive and beyond the means of most patients with OSA. Given the potential therapeutic benefits
and cardiovascular risk reduction, biomedical research into indigenously developing affordable CPAP machines is perhaps the need of the hour.

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Colorectal cancer: Do we now have a definitive screening tool?

Schoen RE, Pinsky PE, Weissfield JL, Yokochi LA, Church T, Laiyemo AO, Bresalier R, Andriole GL, Buys SS, Crawford ED, Foutad MN, Isaacs C, Johnson CC, Reding DJ, O’Brien B, Carrick DM, Wright P, Riley TL, Purdue MP, Izmirlian G, Kramer BS, Miller AB, Googan JK, Prorok PC, Berg CD; PLCO Project Team. (Departments of Medicine and Epidemiology, University of Pittsburgh, and the University of Pittsburgh Cancer Institute, Pittsburgh; Divisions of Cancer Prevention and Cancer Epidemiology and Genetics, National Cancer Institute, and Office of Disease Prevention, National Institutes of Health, Bethesda; Westat and Information Management Services, Rockville, Maryland; Pacific Health Research and Education Institute, Honolulu; Department of Health Studies and Environmental Health Sciences, University of Minnesota, Minneapolis; Department of Medicine, Howard University, and Georgetown University, Washington, DC; M.D. Anderson Cancer Center, Houston; Washington University, St Louis; Huntsman Cancer Institute, University of Utah, Salt Lake City; Anschutz Cancer Pavilion, University of Colorado, Denver; School of Medicine, University of Alabama at Birmingham, Birmingham; Henry Ford Health System, Detroit; Marshfield Clinic Research Foundation, Marshfield, Wisconsin, USA; and Dalla Lana School of Public Health, University of Toronto, Toronto, Canada.) Colorectal cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012; 366:2345–57.

SUMMARY

The PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial is a large, population-based, randomized controlled trial designed and sponsored by the National Cancer Institute of the USA to determine the effect of screening on cancer-related mortality and other secondary end-points in men and women aged 55–74 years. The...