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Editorial

Continuous Positive Airway Pressure Therapy for Metabolic Syndrome in Obstructive Sleep Apnoea: Where Do We Stand?

Non-communicable diseases (NCDs) are responsible for premature deaths and have serious economic consequences globally. In the South-East Asia region of the World Health Organization (WHO), in 2008, NCDs have been recognised to be top killers accounting for 7.9 million deaths with more than one-third (34%) of these occurring in persons aged under 60 years; over the next decade, this number is expected to increase by 21%. The metabolic syndrome (MetS) consists of a constellation of abnormalities that result in an increased risk of coronary artery disease.[1] The key components of the MetS include central obesity, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia, and hypertension. The MetS is emerging as a major public health problem in South-East Asia, especially India.[2]

Obstructive sleep apnoea syndrome (OSAS) affects 2% to 4% of middle-aged men and 1% to 2% of middle-aged women.[3] In a well conducted cross-sectional, community-based, prevalence study from Delhi,[4] the overall prevalence of obstructive sleep apnoea (OSA) and OSAS was found to be 13.7% and 3.8%, respectively. India's population was 1,210,193,422 as per the 2011 Census,[5] of whom middle-aged persons are estimated to constitute approximately 40%. If the average estimate of prevalence of OSAS (i.e., 3% among men and 1.5% among women) is applied to the census data for the year 2011, in terms of absolute numbers, close to 0.75 million men and 0.36 million women would be suffering from OSAS in India. Sleep medicine is an emerging speciality in India and OSA is a major underdiagnosed health problem. Sleep disordered breathing is associated with devastating systemic consequences.[6] Published data from community- and hospital-based studies have revealed a significantly higher prevalence of MetS in patients with OSA in comparison to non-OSA patients.[7]

Both MetS and OSA are known to increase the risk of developing cardiovascular disease.[8] The relationship between MetS and OSA and consequences of MetS in patients with OSA is being extensively studied. Recent evidence suggests that OSA is independently associated with alterations in glucose metabolism and increases the risk of developing type 2 diabetes mellitus. Sympathetic over activity,[9] due to sleep fragmentation and chronic intermittent hypoxia[10,11] are thought to be the key factors responsible for this. Chronic intermittent hypoxia alternating with re-oxygenation cycling is considered to be the hallmark of OSA. These repetitive episodes produce catecholamine surges and oxidative stress mediated immuno-inflammation through activation of transcription factors. These events produce deleterious effects on lipid and glucose metabolism observed in patients with OSA. This effect of chronic intermittent hypoxia is also thought to be related to the weight status both in human and in animal studies.[10,11]

In addition to correction of modifiable risk factors, continuous positive airway pressure (CPAP) is the first-line treatment for symptomatic patients with OSAS.[12] However, the beneficial effect of CPAP on the various components of MetS is still not yet fully understood. Most of the studies assessing the effect of CPAP on the components of MetS have been hampered by a small sample size, a short duration of intervention, and the lack of a control group or a washout period. But for an occasional exception,[13] most of the studies[14-16] have documented a significant lowering of blood pressure with the use of CPAP. Studies assessing the impact of CPAP on lipid profile[12,17-19] have yielded conflicting results with uncontrolled studies documenting a beneficial effect while such an effect was not evident in controlled studies. Data from studies addressing the impact of CPAP on insulin resistance[14,20,21] have also been discordant. Recently published meta-analyses of randomised controlled trials (RCTs) revealed that the effect of CPAP treatment on blood pressure and insulin resistance as measured by homeostatic model assessment for insulin resistance (HOMA-IR) has been modest.[22,23]

A randomised crossover trial[14] did not document a significant reduction in the prevalence of the metabolic syndrome after six weeks of CPAP therapy. Mota *et al*[24] studied the effect of autoadjusting positive airway pressure (APAP) on MetS in 74 male patients with moderate to severe OSA. They reported that, compared with the observations at the baseline, there was a significant decline in the prevalence of MetS six months after APAP (63.5% *versus* 47.3%; p=0.004). In a well-conducted, placebo-controlled, double-blind, randomised, cross-over study with a large sample size and a long follow-up, Sharma *et al*[25] evaluated the effect of three months of therapeutic CPAP followed by three months of sham CPAP, or *vice-versa*, with a washout period of one month in between. Of the 86 patients who completed the study, 75 (87%) had the MetS at the time of recruitment (38 in the CPAP-first group and 37 in the sham CPAP-first group). A reversal in the MetS was observed in 13% of patients undergoing CPAP *versus* 1% in those undergoing sham CPAP. In this study,[25] significant reduction in blood pressure was also documented with the use of CPAP. Furthermore, there was also a significant improvement in the ratio of HDL to total cholesterol and levels of total

cholesterol, triglycerides, and low density lipoprotein and non-HDL cholesterol with CPAP treatment. A significant increase in HDL cholesterol and reduction of carotid intima-media thickness were evident only in patients who were compliant to CPAP treatment. In this study,[25] patients being treated for hypertension, diabetes mellitus, or dyslipidaemia and those with pre-existing cardiovascular disease, nephropathy, or diabetic retinopathy were excluded. In a later randomised, Sham-controlled study, Hoyos *et al*[26] studied 65 nondiabetic CPAP-naive men with moderate to severe OSA. But, they had not systematically exclude patients with other cardiometabolic co-morbidities and patients receiving drug treatment for hypertension and dyslipidaemia. The patients were randomised to receive either real (n=34) or sham (n=31) CPAP for 12 weeks.[26] Thereafter, all subjects received real CPAP for a subsequent period of 12 more weeks. They found no difference in insulin sensitivity, visceral abdominal fat and liver fat in between the groups at 12 weeks. In a recent publication[27] the same group reported that, in these patients, 12 weeks of CPAP therapy had no effect on the development or regression of metS. Contrary to the independent relationship reported in Chinese patients,[28] it was observed that insulin resistance is dependent on obesity rather than OSA in Indian patients.[29] Therefore, racial or ethnic differences among the study populations may have contributed to these differences.

These data, reveal encouraging results with CPAP therapy concerning the components of MetS in patients with OSA and warrant a bi-directional screening for OSA and MetS. The differences in the response of MetS components to CPAP could be related to changes in visceral fat.[8] The relationship between the benefits due to life-style modifying interventions and CPAP; and the obesity-OSA-MetS conundrum seems complex. A multi-modality intervention approach is, therefore, required for benefiting patients with OSA and MetS. The potential therapeutic benefits and the cardiovascular risk reduction with CPAP treatment of OSA should also stimulate biomedical research for indigenously developing affordable CPAP machines in resource-poor countries like India. Future research and RCTs should involve larger sample size for a longer duration and should also try to identify subgroups which derive maximum benefit.

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