Indian J Med Res 131, March 2010, pp 455-458

Are metabolic syndrome, obstructive sleep apnoea & syndrome Z sequential? - A hypothesis

Surendra K. Sharma & Vishnubhatla Sreenivas*

*Departments of Medicine & *Biostatistics, All India Institute of Medical Sciences, New Delhi, India*

Received July 23, 2009

***Background & objectives*: The metabolic syndrome (MS) is a risk factor for development of cardiovascular disease and is closely associated with obstructive sleep apnoea (OSA). Co-occurrence of both OSA and MS is called syndrome Z. It has been hypothesized that the OSA may be a manifestation of MS. We collected data on polysomnography (PSG) and biochemical investigations on middle aged urban Indians during a community based study in South Delhi while studying prevalence of obstructive sleep apnoea and analysed to find out the ages at which the OSA, MS and syndrome Z exist in these subjects.**

***Methods*: A 2-stage, cross-sectional, population-based study in subjects of either gender between 30-65 yr of age in 4 different socio-economic zones of the South Delhi, India, was performed earlier (from April 2005 through June 2007). In-hospital, supervised PSG studies were performed and biochemical investigations for the MS using National Cholesterol Education Programmme Adult Treatment Panel (NCEP ATP) III criteria were carried out. In this communication, the data were further analysed to estimate the prevalences of MS alone, OSA alone and syndrome Z and average ages of 3 conditions.**

***Results*: Three hundred and fifty one subjects had satisfactory PSG studies. The MS alone was present in 105 [29.9%; (95% CI 25.1-34.7)] while OSA alone was present in 24 [6.8%; (95% CI 4.2-9.5)] subjects and the syndrome Z was present in 70 [19.9%; (95% CI 15.8-24.1)] subjects. Median ages of normal subjects, and subjects with MS, OSA and syndrome Z were 40, 43, 43 and 47 yr respectively. Minimum ages of normal subjects, and subjects with MS, OSA and syndrome Z were 30, 30, 32 and 32 yr respectively.**

***Interpretation & conclusions*: When body mass index (BMI) was normal, the increasing median ages of these conditions indicated that the MS may be the first event followed by OSA and eventually syndrome Z develops. With BMI >25 or >30 no clear-cut difference was noted, indicating that the BMI itself could have an independent role in MS, OSA and syndrome Z.**

Key words Metabolic syndrome - obstructive sleep apnoea - prevalence - South Asians - Indians - syndrome Z

Metabolic syndrome (MS) is characterized by hypertension, abdominal obesity, increased triglycerides and blood glucose and decreased HDL cholesterol[1,2] and is associated with an increased risk for the development of type 2 diabetes mellitus[3] and cardiovascular disease[4]. Several studies suggest that the prevalence of MS according to National Cholesterol Education Programme Adult Treatment Panel

(NCEP-ATP) III criteria is about 40 per cent greater in obstructive sleep apnoea (OSA)[5]. Though there is circumstantial evidence to implicate OSA in the development of MS, the causal relationship, remains unproven. Animal studies suggest that diabetes may lead to a marked depression in ventilatory control mechanisms[6]. It has been hypothesized that in the setting of OSA and MS, there probably exists feedforward relationship between the two which leads to further aggravation of both disorders. It has been proposed that the OSA may be one of the manifestations of MS[7,8]. Though several human studies suggest that the OSA is independently associated with insulin resistance and other components of the MS, published data are conflicting[9-14]. Syndrome Z (SZ) is defined as the co-occurrence of OSA and metabolic syndrome[15].

In the present study we analysed the data collected in a community based study in South Delhi, India, to determine the ages at which the three conditions, MS, OSA or syndrome Z exist in subjects undergoing sleep studies. The data were stratified according to BMI <25, > 25 and ≥ 30 kg/m^2, using 2 cut off values, 25 and 30 of BMI.

Material & Methods

Study population, polysomnography studies and investigations for MS: The South Delhi sleep study was a two-stage cross-sectional study aimed at determining the prevalence and risk factors for OSA in middle-aged urban Indians. The study design and recruitment of subjects are detailed elsewhere[16].

A total of 365 subjects consented and underwent in hospital polysomnography (PSG), detailed anthropometry and blood pressure recording made as described previously[16]. Polysomnography studies were scored manually according to standard criteria by trained technicians[17,18]. The OSA was defined as apnoea-hypopnoea index (AHI) > 5. Various biochemical investigations were carried out in these subjects as described previously[19]. At the end of the sleep study on the next morning fasting blood samples were taken from each subject for the following biochemical tests: blood sugar (glucose oxidase method) and lipid profile (total cholesterol, LDL, HDL cholesterol and triglycerides). Total cholesterol, triglycerides and HDL-cholesterol were measured using immunocolorimetric assay while LDL-cholesterol was derived indirectly using the Freidwald equation[20].

Metabolic syndrome: The MS was defined according to NCEP-ATP III[21] criteria. The cut-offs for defining abdominal obesity based on waist circumference were taken as > 90 cm in males and > 80 cm in females[22]. Likewise, a lower cut-off of BMI (25) was used to define obesity[23]. Subjects having 3 of 5 criteria were said to have MS.

The magnitude of the three conditions and the minimum and median ages of the three groups (MS, OSA, SZ) were compared to get an idea about the sequence of the three events. Box-plots were constructed using Stata 9.2 (Stata Corporation Inc. College Station, Texas, USA). Comparison of clinical and laboratory parameters among various group was done by One-way ANOVA.

Results & Comment

The Table provides comparison of clinical and laboratory parameters among four groups in 351 subjects. The MS was observed in 105 [29.9% (95 % CI 25.1-34.7)] of the subjects studied while the OSA

Table. Comparison of clinical and laboratory parameters among various groups

Component	Normal (n=152)	Metabolic syndrome (n=105)	Obstructive sleep apnoea (n=24)	Syndrome-Z (n=70)	*P* value*
Fasting blood sugar (mg/dl)	97.3 ± 32.9	110 ± 39.9	94 ± 9	108.5 ± 38.4	0.01
Serum cholesterol – total (mg/dl)	191.3 ± 41.6	212.3 ± 44.5	197.6 ± 48	214.4 ± 47.7	<0.001
Triglycerides (mg/dl)	133.4 ± 52.9	193.8 ± 69.3	141 ± 48.6	204.3 ± 78.8	<0.001
Serum HDL (mg/dl)	52 ± 9.6	45.4 ± 10.3	55 ± 16.1	40.9 ± 9.3	<0.001
Serum LDL (mg/dl)	112.6 ± 38	128.1 ± 38.8	114.3 ± 44.3	132.7 ± 39.6	<0.001
Waist circumference (cm)	90.6 ± 13.3	99 ± 10	105.4 ± 20.4	109 ± 11.2	<0.001
Systolic BP (mm Hg)	124.8 ± 11.1	137.9 ± 18.6	129.8 ± 14.3	140.1 ± 17.1	<0.001
Diastolic BP (mm Hg)	82 ± 8.9	90.8 ± 12.4	85.8 ± 6.3	91.6 ± 12.5	<0.001
Apnoea-hypoapnoea index (events/h)	0.5 ± 1.1	0.9 ± 1.3	24.8 ± 18.3	33.2 ± 26.12	<0.001
BMI (kg/m^2)	24.76 ± 5.63	28.24 ± 4.27	28.58 ± 8.39	31.73 ± 5.62	<0.001

*By one-way ANOVA

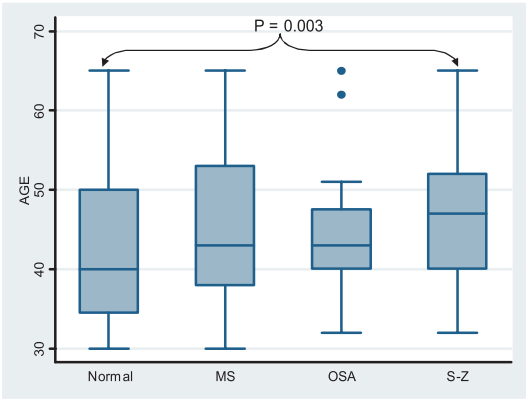
and syndrome Z were seen in 24 [6.8% (95% CI 4.2-9.5)] and 70 [19.9% (95% CI 15.8-24.1)] individuals respectively.

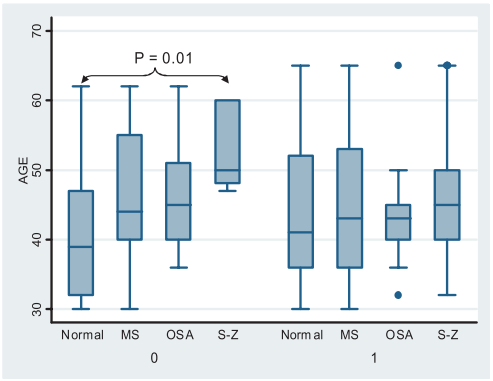
The ages of the subjects in the four groups (Fig. a) showed that the medians age increased from 40 yr among normal subjects to 47 yr among the subjects with syndrome Z. The two groups of subjects with MS alone and OSA alone had similar median age of 43 yr. Gradual increase in the median ages of four groups were observed among those with BMI < 25 (kg/m^2) (39, 44, 45 and 50 yr) in the four groups of normal, MS alone, OSA alone and SZ respectively) (Fig. b). The minimum ages also showed similar trend of the subjects in the 4 groups *i.e.* 30, 30, 36 and 47 yr respectively. Among persons with BMI >25, the differences in the median ages among the 4 groups were less distinct, namely 41, 43, 43 and 45 yr respectively, while the minimal ages were 30, 30, 32 and 32 yr respectively (Fig. b).

In the morbidly obese group (BMI ≥ 30), the median ages of MS alone and OSA alone groups were 2 and 3 yr lesser than that of normal persons whose median age was 45 yr. The minimal ages observed among the 4 groups were 30, 30, 40 and 34 yr respectively (Fig. c).

The decreasing magnitude of the three conditions together with the increases in median and minimum ages observed, indicate that in the spectrum of developing syndrome Z, MS is the first followed by OSA. However, among those who are morbidly obese (according to the lower cut-off of BMI as recommended by WHO for the south Asian countries), this distinction seems to be less clear. This might be attributed to the presence of other co-morbidities such as diabetes mellitus, hypertension which are more frequent among excessively obese persons.

In conclusion, findings of this study provide an indication that in subjects with normal BMI, MS develops first followed by OSA. The biological significance of these results is not clear at present. It is plausible that differential activation of selective genes may be possible through gene environment interaction and appearance of these conditions. Being a cross-sectional in nature, this study can not answer a temporal relationship definitively. To have a better understanding about which occurs first before a person develops syndrome Z, a well-planned cohort study on presently normal individuals with regular monitoring including polysomnography and various metabolic parameters is required. This is an important issue





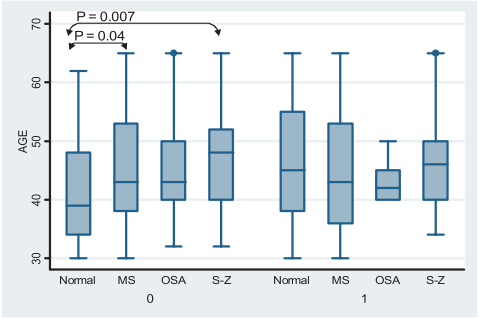


Fig. a. Box plots showing ages (median and ranges) in normal subjects, and subjects with MS, OSA and syndrome Z. **Fig. b.** Box plots showing ages (median and ranges) in normal subjects, and subjects with MS, OSA and syndrome Z according to BMI <25 and > 25 kg/m^2. **Fig. c.** Box plots showing ages (median and ranges) in normal subjects, and subjects with MS, OSA and syndrome Z according to BMI <30 and >30 kg/m^2.
BMI, body mass index; MS, metabolic syndrome alone; OSA, obstructive sleep apnoea alone; S-Z, syndrome Z.

for the future research as the prevalence of obesity is increasing worldwide and with this increase the prevalence of OSA, MS and syndrome Z will also increase tremendously. This will require urgent public health intervention strategies otherwise health resources of the developing and developed nations will be overburdened.

***Conflict of interest*:** None

Acknowledgment

Authors thank sleep laboratory technicians, Shriyuts Jitender Sharma, Jitender Kumar and Hridesh; Kuldeep and Santosh for their assistance in data collection. Authors also thank Shri Hemant Kumar Mishra for going through the manuscript. Authors thanks Pfizer India Ltd. for financial support.

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Reprint requests: Dr S.K. Sharma, Chief, Division of Pulmonary, Critical Care & Sleep Medicine, Head, Department of Medicine
All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: surensk@gmail.com, sksharma@aiims.ac.in