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Original Research

Prevalence of syndrome Z among coronary artery disease patients attending a tertiary care hospital in south India

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Abstract

Introduction: Metabolic syndrome (MS) and obstructive sleep apnea (OSA) trigger the development of coronary artery disease (CAD). This study aims to estimate the prevalence of syndrome Z (metabolic syndrome + obstructive sleep apnea) among CAD patients. **Materials and Methods**: OSA was assessed based on a modified Berlin questionnaire and metabolic syndrome was identified based on National Cholesterol Education Program Adult Treatment Panel III guidelines. Anthropometric assessment and blood pressure were recorded. Serum triglyceride, high-density lipoprotein level (HDL), and fasting blood glucose levels were estimated. **Results**: Syndrome Z was prevalent among 51% of CAD subjects. The other groups were CAD only, CAD with MS, and CAD with OSA. All data were compared using one-way ANOVA followed by Tukey's multiple comparisons. Blood pressure, triglyceride, and HDL showed a significant F test ratio. Post hoc test showed CAD subjects with syndrome Z had significantly higher mean levels of systolic BP (140.30±17.94) (p=0.001), diastolic BP (89.09±11.82) (p=0.003), triglyceride (232.73±107.71) (p=0.000) and HDL levels (33.22±6.46) (p=0.000) compared to other groups. **Conclusion**: Concurrent presence of OSA and MS has an adverse cardio-metabolic outcomes. Identifying the presence of OSA and appropriate treatment at early stages can prevent the development of CAD to an extent.

Keywords: syndrome Z, metabolic syndrome, obstructive sleep apnea, coronary artery disease.

Background and aims

Cardiovascular diseases have been identified to be one of the leading causes of death accounting for 17 million deaths per year and are expected to become 24 million in another decade [1]. The prevalence of coronary artery disease (CAD) in India is 8–10% [2]. In the urban south Indian population prevalence of CAD is reported to be 11% [3]. Extensive research has been put forth to identify the risk factors involved in CAD occurrence and measures to curtail them. The important pathophysiological mechanisms involved in cardiovascular diseases are hypoxia followed by reperfusion generating reactive oxygen species (ROS) leading to oxidative stress, endothelial dysfunction and systemic inflammation, sympathetic hyper-activation causing hypertension and vasoconstriction, development of the hyper-coagulable state, metabolic dysregulation producing insulin resistance and dyslipidemia [4–7]. A confluence of the above-mentioned

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pathological processes constitutes metabolic syndrome (MS) or syndrome X [8].

According to WHO criteria, metabolic syndrome is defined by the presence of diabetes or impaired glucose tolerance or insulin resistance plus two or more of the following criteria: body mass index (BMI) >30 kg/m^2 or waist–hip ratio >0.9 in men, >0.85 in women, triglycerides ≥150 mg/dl, high-density lipoprotein (HDL) <35 mg/dl in men and <39 mg/dl in women, blood pressure ≥140/90 mm/Hg or on anti-hypertensive, urine albumin excretion ≥20 µg/min [9]. In Asian population, National Cholesterol Education Program (NCEP) - *Adult Treatment Panel* (ATP III) criteria has been identified to be validated definition which includes presence of any three of the following five criteria such as waist circumference >102 cm in men, >88 cm in women, triglycerides >1.7 mmol/l (>150 mg/dl), HDL cholesterol <1.03 mmol/l (40 mg/dl) in men and <1.29 mmol/l (43 mg/dl) in women, blood pressure >130/85 mm/Hg or on anti-hypertensive, plasma fasting glucose > 6.1 mmol/l (100 mg/dl) or on anti-diabetic treatment [10]. Prevalence of metabolic syndrome as per WHO criteria is 21.2% whereas as per NCEP ATPIII 2001 criteria is 16.7% [11, 12].

The above pathological mechanisms leading to metabolic dysregulation and in turn to CAD are also triggered by sleep disturbances and sleep-disordered breathing [13, 14]. Obstructive sleep apnea (OSA) is a type of sleep-disordered breathing in which there is an obstruction to the upper airway during sleep [13]. Occurrence of OSA peaks in middle-aged subjects and declines after 65 years. The prevalence of OSA in adult men is 3–7% all over the world [13]. The prevalence of OSA in middle-aged Indian adult men was found to be between 9–13% [15, 16]. Clinically OSA can be defined as repeated occurrence of apnea and hypopnea during sleep with occasional quitting of breath [7]. Repeated hypoxia followed by re-oxygenation during sleep also triggers the generation of reactive oxygen species (ROS) which produce oxidative stress and endothelial damage by the production of inflammatory markers particularly affecting the coronary vasculature triggering the development of atherogenic plaque [13, 17]. Overnight polysomnography is the gold standard diagnostic method to identify the presence of OSA [18]. OSA is a complex disorder with multiple risk factors the most common being obesity with central adiposity and increased neck circumference causing pressure on upper airway structures in supine position making it more vulnerable for easy collapsibility during sleep [19]. Further, sympathetic over-activation that occurs in chronic OSA due to prolonged exposure to hypoxic states results in increased systolic arterial blood pressure and hypertension [20, 21]. Chronic intermittent hypoxia also triggers renin release which in turn causes further sympathetic activation [22]. Studies have shown that chronic intermittent hypoxia and oxidative stress lead to lipid peroxidation and alteration in the lipid biosynthetic pathway resulting in dyslipidemia [23]. In addition, sleep fragmentation, sleep loss (common features of OSA), alteration in hypothalamic-pituitary axis and increased production of cytokines have been identified as independent markers of altered glucose metabolism leading to insulin resistance and diabetes mellitus [24, 25].

The concurrent existence of metabolic syndrome and OSA is termed as syndrome Z which serves to impose an additional threat on cardiovascular outcome [26]. Increased incidence of both metabolic syndrome and OSA in the general population has led to a corresponding increase in the prevalence of syndrome Z. A pilot study in Singapore has shown the prevalence of syndrome Z to be 88% [27]. The estimated prevalence of syndrome Z in urban north Indian population was 4.5% [28]. Further, recent studies have identified south India as a hub for major cardiovascular risk factors particularly dyslipidemia and diabetes mellitus [12]. Hence this study was initiated to identify the prevalence of syndrome Z among coronary artery disease patients attending a tertiary care hospital in a semi-urban part of south India and to identify the major cardio-metabolic risk factors.

Methods

Study design and patients

This is a cross-sectional study conducted in a private hospital in the semi-urban sector of south India on patients attending the cardiology department. Institutional ethical clearance was obtained. All male subjects with documented coronary artery disease were included in this study. Subjects with cardiac disorders other than CAD such as congenital, valvular, or cyanotic diseases and other sleep-related disorders such as central sleep apnea, insomnia, hypersomnolence were excluded from the study. Informed consent was obtained from the subjects after explaining to them in their vernacular language. Socio-demographic data and family history of either OSA or CAD were also obtained. These subjects were administered a modified Berlin questionnaire [29], which is a validated tool with sensitivity and specificity of 86% and 95%, respectively [29], to assess the risk of OSA. They were guided to fill out the questionnaire along with their bedtime partner. In brief, the questions were grouped into three categories, first one was to identify the presence of snoring and the frequency and loudness of snoring. Questions in the second category helped to identify the presence of excessive tiredness and daytime sleepiness and the third category was to identify the presence of hypertension (blood pressure ≥130/85 mm Hg) or obesity (BMI ≥25). Subjects with positive response in a two or more categories were considered high risk for OSA and the rest were grouped as low risk [29].

Laboratory, anthropometric and clinical data collection

Anthropometric measurements were recorded according to standard guidelines with the subject wearing light clothing. Weight (kilogram) was measured nearest to 100 mg on a digital scale and height (centimeters) was measured maintaining the Frankfurt plane to the nearest 0.1 cm. Body mass index was calculated by using the formula BMI=weight (in kg)/ (height*height) (m^2). Waist circumference (centimeters) was measured at the level of the umbilicus. Blood pressure was recorded in the right arm in a sitting position using a digital sphygmomanometer. Three consecutive recordings were made with 5 minutes intervals and the maximum reading was considered.

All blood parameters were analyzed using an RXL dimension auto analyzer. Serum triglyceride (TGL) levels were estimated using the lipase method, fasting blood glucose (FBG) levels were estimated by hexokinase method and high-density lipoproteins (HDL) were estimated by precipitation method and all values were recorded in mg/dl.

The presence of coronary artery disease was confirmed by a coronary angiogram done by the cardiologist. The procedure was performed in a specifically designed cathlab and recordings were made using a cardioangiograph. The percutaneous transfemoral approach was routinely used for cardiac catheterization. The potential access sites were shaved, cleaned, and disinfected. Local anesthesia was applied, with 10–15 ml of 2% lidocaine for local infiltration of the skin and subcutaneous tissues. The standard technique of arterial puncture called the Seldinger technique was used. Specifically designed diagnostic catheters were advanced into the right atrium via inferior vena cava, and radiocontrast was applied. Under fluoroscopic guidance, the catheter was advanced into the coronary ostium, and several recordings of the left coronary artery and right coronary artery and its branches were taken. The presence of atheromatous plaques in any one of the coronary arteries by this technique confirmed the presence of CAD in these subjects. Presence of metabolic syndrome was identified based on NCEP ATP III guidelines [10].

Statistical analysis

Statistical analysis was done using SPSS version 17. The CAD subjects were grouped based on the presence of either OSA or metabolic syndrome or both into four groups viz., CAD only, CAD with metabolic syndrome, CAD with only OSA and CAD with syndrome Z (CAD+OSA+MS).

Results

This study estimated a prevalence of 51% syndrome Z (OSA+MS) among CAD subjects. The

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other groups had the following distribution – CAD only (17.9%), CAD with MS (10.4%), CAD with OSA (20.9%). All data collected were compared between these four groups using one-way ANOVA followed by Tukey's multiple comparisons.

Blood pressure, both systolic and diastolic pressure, showed a significant F test ratio. Post hoc test revealed that means of systolic blood pressure were significantly higher than CAD only group in both CAD with OSA group (p=0.014) and CAD with syndrome Z group (p=0.001). The increase in systolic blood pressure in the CAD with syndrome Z group was significantly higher than that seen in the CAD with OSA group (p=0.014). A similar observation was made for the diastolic blood pressure as well (Table 1).

Among biochemical parameters estimated, serum triglycerides and high-density lipoprotein showed a significant F test ratio. Post hoc test showed that means of triglyceride levels of both CAD with OSA group (p=0.000) and CAD with syndrome Z group (p=0.000) were significantly higher than CAD only group. Likewise, both CAD with OSA group (p=0.006) and CAD with syndrome Z group (p=0.000) revealed significantly high mean values when compared with CAD with MS group. Post hoc comparison of mean high-density lipoprotein levels was low among CAD with OSA group (p=0.003) and CAD with syndrome Z group (p=0.000) when compared with other groups.

Discussion

This study has estimated a very high prevalence of syndrome Z among CAD subjects which is in tandem a previous study that showed a 59% prevalence of syndrome Z among subjects posted for maxillofacial surgery [30]. Both OSA and metabolic syndrome have been identified to be independent risk factors for the development of CAD and hence co-existence of both has contributed to a higher prevalence rate as observed in this study. Further, it was also observed that both metabolic syndrome and OSA were highly prevalent among CAD subjects when compared to earlier studies. The presence of hypertension is independently identified to be associated with both metabolic syndrome and OSA [20, 31, 32] which is reflected in this study also. This study showed a statistically significant increase in both systolic and diastolic blood pressure among CAD subjects with syndrome Z. Chronic intermittent hypoxia produced by OSA causes sympathetic hyperactivity and triggers the release of inflammatory markers which cause vascular endothelial damage [32]. Reports have shown that a nocturnal dipping pattern in blood pressure recording is missing in subjects with OSA [20]. In addition, studies have also observed increased urinary levels of catecholamine particularly noradrenaline in patients with OSA [33]. These could have probably resulted in the elevated blood pressure

Table 1: Comparison of mean and analysis of variance of parameters of metabolic syndrome among the four groups.

Parameters	CAD (n=12)	CAD+MS (n=7)	CAD+OSA (n=14)	CAD+OSA+MS (CAD+syndrome Z) (n=34)	F test ratio
Systolic BP (mm Hg)	132.35±19.80	135.00±18.62	137.36±18.62*	140.30±17.94*@	6.965$
Diastolic BP (mm Hg)	84.47±12.68	86.36±12.22	87.36±12.11*	89.09±11.82*@	7.635$
Waist circumference (cm)	91.71±13.55	92.57±14.36	94.53±15.15	94.00±15.52	2.675
Triglycerides (mg/dl)	197.65±94.56	222.31±96.13	217.33±107.05*#	232.73±107.71*#	13.612$
High density lipoprotein (mg/dl)	34.87±6.62	32.90±6.14	34.61±6.88*#	33.22±6.46*#	15.329$
Fasting blood glucose (mg/dl)	126.17±24.86	130.13±24.39	128.28±24.79	129.00±25.13	2.544

One-way ANOVA followed by post hoc Tukey multiple comparison done. df (3, 63). p<0.05 when compared with *CAD only, #CAD and MS, @CAD and OSA. $ indicates p<0.05.
*Significance. CAD: Coronary Artery disease, MS: Metabolic syndrome, OSA: Obstructive Sleep Apnea.

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in CAD subjects with syndrome Z as observed in this study.

OSA is also associated with altered lipid biosynthetic pathways. Chronic intermittent hypoxia causes upregulation of genes involved in the production of substrates for lipid biosynthesis [23]. This is reflected in the current study by the significantly increased level of serum triglycerides among subjects with syndrome Z. High-density lipoprotein plays a major role in the transfer of cholesterol esters from the periphery to the liver for their breakdown and efflux of cholesterol from endothelial cells of the arterial wall [34]. Additionally, HDL has an anti-oxidant effect that prevents LDL oxidation and thus prevents the formation of atherogenic plaques [35]. OSA causes a reduction in high-density lipoprotein levels thereby promoting the formation of atherosclerosis [23]. Cyclical hypoxia and re-oxygenation induces a form of oxidative stress which constitutes an important mechanism for the development of insulin resistance and diabetes [25, 36]. Sleep duration and sleep quality have been identified to impact blood glucose levels. About 15–30% of incident diabetes has been reported in subjects with reduced sleep duration up to 6 hours and 50% increased incidence of diabetes among subjects who had difficulty in initiating sleep [36]. This study failed to show a significant increase in fasting blood glucose level which could be attributed to anti-diabetic treatment which tends to maintain plasma fasting blood glucose levels within the normal range. The key measures identified in this study are high blood pressure, increased triglyceride level and decreased high-density lipoprotein. Hence these risk factors need to be taken into consideration during CAD risk stratification along with the determination of risk for OSA using simple questionnaire.

This study has been conducted in a hospital setting on only male subjects and the determination of OSA restricted to questionnaire instead of the gold standard diagnostic method of overnight polysomnography (PSG). Studies have shown a 57% prevalence of syndrome Z among females [37], hence future studies could be planned on both the sex and overnight PSG can be used for confirmation for the presence of OSA.

Conclusion

The presence of OSA has adverse effects on cardiovascular events. Preliminary screening for OSA can be done using simple a questionnaire and used for stratification of patients along with biochemical and anthropometric measurements. Treatment for OSA based on confirmation of its presence would probably play a key role in CAD management.

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Conflict of interest

The authors declare no conflict of interest.

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