Prevalence and Clinical Profile of Syndrome Z in Type 2 Diabetes Mellitus

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ABSTRACT

Background : Syndrome Z constitutes Metabolic Syndrome (MS) and Obstructive sleep apnea (OSA). This study aims to find prevalence of Syndrome Z in Type 2 Diabetes Mellitus (T2DM) and its correlation with cardio metabolic risk factors.

Methods : In this cross sectional Observational study 134 patients of T2DM were assessed by NCEP ATP III criteria for Metabolic Syndrome and Berlin questionnaire for OSA. Patients having high risk for OSA and MS were diagnosed to have Syndrome Z. Sleep studies were conducted. Cardiometabolic risk factors were compared in those with and without Syndrome Z. Univariate and multivariate statistical Analysis was done.

Results : Of 134 diabetics, 48 (35.8%) had MS and 66 (49.2%) had OSA of which 32 (23.9%) were high risk and 34 (25.4%) low risk. 37 (27.6%) had Syndrome Z. The mean age was 58.32 ± 9.35 years with M: F ratio of 1: 1.06. Mean duration of Diabetes was 9.63 ± 3.92 years ($p < 0.001$). Significant cardio metabolic risk factors were Hypertension; $p=0.034$ and positive family history of CAD; $p = 0.046$.

There was a positive correlation of BMI with MS; $r = 0.38$, OSA; $r = 0.40$ and maximum for Syndrome Z; $r = 0.57$. Mean serum triglycerides and waist circumference were significantly more($p=0.01$).

Conclusion : The prevalence of Syndrome Z is high in T2DM, and increases with age and duration of Diabetes. Hypertension is an independent risk factor. Syndrome Z has a positive correlation with BMI, Hypertriglyceridemia, and increased waist circumference.

Background :

Syndrome Z is defined as the co-occurrence of obstructive sleep apnea (OSA) and metabolic syndrome. There is paucity of information on the magnitude of Syndrome Z in the community and the factors associated with it[1].

Obstructive sleep apnea (OSA) has been linked to increased cardiovascular morbidity and mortality from both coronary heart disease and stroke[2] but whether this risk is due to coexistent known cardiovascular risk factors or specific effects of OSA remains to be established. Patients with OSA have many features in common with those with syndrome X, including systemic hypertension which is commonly reported[3], patients are typically overweight (usually with a central pattern[4,5] and insulin resistance based on clinical diabetes or measured insulin resistance is well documented[6]). Dyslipidemia (mixed elevation of cholesterol and triglycerides) has not been extensively studied in OSA but, since this pattern of lipid abnormality reflects resistance to lipoprotein lipase which is partly dependent on insulin, it too is likely to be present.

Thus, "Metabolic syndrome (MS) or Syndrome X" may include OSA and could be better considered as "syndrome Z"[7]. Features of "syndrome Z" include Hypertension, Central obesity, Insulin resistance, Hyperlipidemia and Obstructive sleep apnea.

Only a few studies in India have studied the prevalence of Syndrome Z in type 2 diabetics. Hence this study was carried out to study the prevalence of Syndrome Z in T2DM patients and to study its correlation with various cardiometabolic risk factors.

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Aims and Objectives

Primary aim :

1. To study prevalence and clinical profile of Syndrome Z (OSA and MS) in patients of T2DM
2. To study the correlation of morphological and biochemical parameters of MS with Syndrome Z in T2DM.

Secondary aim : To correlate the cardio metabolic risk factors like age, smoking, hypertension, obesity, hyperlipidemia, with Syndrome Z.

Materials and methods :

This Cross Sectional, Observational study was carried out over a period of 2 months in the Diabetes Clinic of a tertiary care center at Nagpur. Study was initiated after taking approval from Institute's Ethics Committee. We screened 134 cases of which 94 were taken for final analysis.

CASES : 37 consecutive cases of T2DM as defined by American Diabetes association (ADA) criteria attending the diabetes clinic who were diagnosed to have Syndrome Z (MS+OSA)

Controls or Comparators : 57 consecutive patients of T2DM having neither MS nor OSA.

Following patients were excluded from the study; those having Chronic Obstructive Pulmonary Disease (COPD), taking drugs which cause bronchoconstriction, like beta-blockers, cholinergic etc., Myocardial infarction, Stroke, Percutaneous Trans luminal Coronary Angioplasty (PTCA) or Coronary artery bypass graft in last 3 months, secondary hypertension, clinically apparent heart failure, Type 1 diabetes mellitus, Comorbidities with bad prognosis (death expectation > 30%), and pregnant women.

Methodology :

Patients attending the diabetic clinic of our hospital, satisfying inclusion criteria were selected. Informed written consent was taken. A detailed history was taken including diabetic history.

Clinical examination was done. All patients were assessed according to the NCEP ATP III criteria (The US National Cholesterol Education Program Adult Treatment Panel III) for the diagnosis of Metabolic Syndrome. All patients were asked questions from the Berlin questionnaire for the diagnosis of OSA. Polysomnography is the gold standard test for OSA diagnosis, but requires overnight evaluation. The Berlin questionnaire (BQ), which includes questions about snoring, daytime somnolence, body mass index (BMI), and hypertension, is a brief and validated screening tool that identifies persons in the community who are at high riskfor OSA8. According to Berlin questionnaire, patients were classified into high risk- 2 or more categories where the score is positive and low risk - only 1 or no category where the score is positive, type of OSA (if diagnosed). Polysomnography was done in selected patients if the diagnosis of OSA was doubtful. Blood sample was collected for lipid profile and fasting glucose levels. NCEP ATP III criteria were used for the diagnosis of metabolic syndrome: 5Following clinical and biochemical parameters were assessed :

1. Waist circumference
2. BMI
3. Blood pressure
4. Serum triglyceride
5. Fasting plasma glucose

The patients were divided into two groups :

1. Patients having Syndrome Z i.e. Metabolic Syndrome and OSA
2. Patients not having Syndrome Z i.e. No MS or OSA. Comparisons were made according to baseline characteristics, risk factors, and clinical profile which included diabetic status, symptomatology, morphological characteristics and biochemical parameters.

Statistical Analysis - Data was entered using the Microsoft excel program. Data was quoted as mean values with the standard deviation. Analysis was done by statistical software Open Epi Info version 2.3 - 2009. Data was compared using Students't - Test for continuous variables and chi square test for categorical variables as appropriate. $P<0.05$ was considered statistically significant.

Results :

Total No. of patients screened in the study : n=134

No. of patients with Metabolic Syndrome (MS) : n=48 (35.8%)

No. of patients with Obstructive Sleep Apnea (OSA) : n=66 (49.2%)

No. of patients with Syndrome Z (MS and OSA) = 37 (27.6%)

No. of patients without Syndrome Z (No MS/OSA) = 57 (42.5%)

Effective sample size for analysis n= 94 (excluding patients who have either MS/OSA n=40)

(Figure 1 & 2)

Figure 1 : **Study design and process**

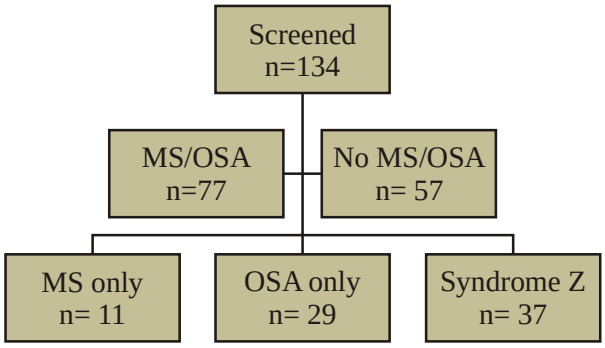
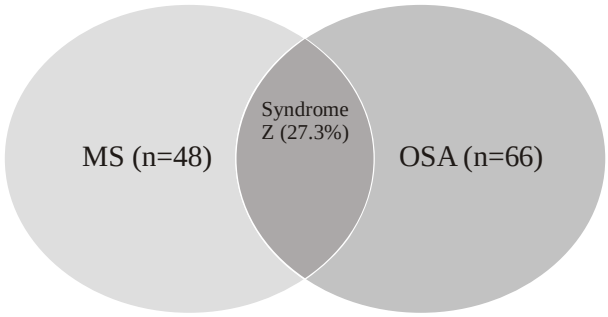


Figure 2 : **Showing prevalence of Syndrome Z**



Comparison of baseline characteristics as shown in ***Table 1*** revealed that there was no statistically significant difference in mean age and gender but as the age advanced, prevalence of Syndrome Z increased.

Most of the Cardio-metabolic risk factors were observed with equal frequency in both groups. There was a significant correlation between Hypertension (p=0.034), Positive family history for Coronary artery disease (p value = 0.046) and Syndrome Z on univariate analysis. On multivariate analysis, Hypertension was found to be an independent risk factor for syndrome Z, p<0.05. As the number of risk factors increased, prevalence of Syndrome Z also increased significantly. Except for hypertension other co morbidities occurred with similar frequency in both groups ***(Table 2)***.

Table 1 : **Baseline characteristics in study population**

Baseline characteristics	**Syndrome Z (n=37)**	**No Syndrome Z (n=57)**	**p-value**
Mean Age + SD	58.32 ± 9.35	60.61 ± 8.15	0.73
M: F	1: 1.06	1: 0.58	0.16
CV Risk Factors			
Nil	9 (24.3%)	15 (26.3%)	0.89
Smoking	2 (5.4%)	nil	0.91
Alcoholism	2 (5.4%)	2 (3.5%)	0.5
Hypertension	18 (48.6%)	13 (22.8%)	0.034, S
Sedentary work	16 (43.2%)	30 (52.65)	0.07
Positive Family history of CAD	15 (40.5%)	18 (31.5%)	0.046, S
Diabetes status			
Duration in years (Mean ± SD)	9.63 ± 3.92	4.42 ± 2.33	p<0.001
Treatment OHA	29 (78.4%)	51 (89.5%)	0.14
Insulin	8 (21.6%)	6 (10.5%)	
Compliance Regular	26 (70.3%)	49 (86%)	0.16
Irregular	11 (29.7%)	8 (14%)	

Table 2 : **Comorbidities and Syndrome Z**

Comorbidities		
Co-morbidity	**Syndrome Z (n=37)**	**No Syndrome Z (n=57)**
No comorbidity	3 (8.1%)	11 (19.3%)
HT	18 (48.6%)	13 (22.8%)
AMI	4 (10.8%)	2 (3.5%)
IHD	8 (21.6%)	13 (22.8%)
PVD	2 (5.4%)	Nil
CVE	2 (5.4%)	1 (1.8%)
Total	**37**	**57**

Comparison of Diabetes status revealed that the mean duration of diabetes was more in patients with Syndrome Z, i.e. 9.63 ± 3.92 years as compared to those without Syndrome Z, i.e. 4.42 ± 2.33 years, and this difference was statistically significant **(p value < 0.001).** There was no significant difference as far as diabetes treatment was concerned (p value = 0.14). But the compliance to treatment was relatively poor in patients with Syndrome Z i.e. 70.3% vs. 86% (p value = 0.064) ***(Table 1).***

Evaluation of risk for OSA by Berlin's questionnaire revealed that snoring was a very commonly observed symptom in both groups. But associated symptoms like daytime sleepiness, lack of concentration were more commonly seen in patients with syndrome Z. However, this difference was not statistically significant **(p value = 0.1760)** (χ^2 = 4.943, df=3).

Comparison of morphological characteristics showed that the mean height of patients in Syndrome Z was slightly lower than that in patients without Syndrome Z, though statistically insignificant (p value = 0.54). The mean weight of patients in Syndrome Z was significantly higher than that in patients without Syndrome Z **(p value< 0.001).** BMI was also significantly higher and correlated positively with MS (r=0.38), OSA (r=0.40) and Syndrome Z (r=0.57). The mean waist circumference of patients of Syndrome Z was significantly higher than those without; males as well as females **(p value < 0.001).** BMI, weight and waist circumference was significantly higher in Syndrome Z than MS or OSA alone.

On comparison of blood glucose and lipids it was observed that the mean TGL levels were significantly higher in Syndrome Z patients as compared to patients without Syndrome Z **(p value = 0.01).** But the mean HDL levels were slightly lower but statistically insignificant, in patients with Syndrome Z ***(Table 3)***

Table 3 : **Comparison of morphological and biochemical parameters in Syndrome Z**

Parameter	**Syndrome Z (n=37)**	**OSA/MS alone (n=40)**	**No Syndrome Z (n=57)**	**P value**
Morphological				**0.54**
Height in cm	156.91 ± 9.04	162 + 7.43	158.22 ± 10.83	
Weight in Kg	72.48 ± 10.33	67.7 + 5.71	60.5 ± 9.11	< **0.001**
BMI Kg/m^2	29.59 ± 4.58	27.29 + 3.52	24.23 ± 3.21	< **0.001**
Waist Circumference				
Males	95 ± 7.13	94.4+ 8.8	88.01 ± 8.07	< **0.001**
Females	93.58 ± 6.06	90.63 + 7.9	81.95 ± 6.94	< **0.001**
Biochemical				
FBS	137.92 ± 51.87	140 + 33.81	133.86 ± 51.79	0.71
PMBS	212.55 ± 73.41	194.30 + 25.5	198.24 ± 63.8	0.31
TGL	144.96 ± 96.71	138.43 + 64.7	137.1 ± 67.16	**0.01**
HDL	46.78 ± 13.18	44. 52 + 18.3	48.88 ± 15.55	0.49

Correlation coefficient for BMI : MS = 0.38OSA= 0.40Syndrome Z= 0.57

Discussion :

Obstructive sleep apnea affects approximately 10% of middle-aged men and 5% of women and is therefore a common condition. Association of Metabolic syndrome with T2DM has also been well established. OSÁ has been known to occur with increased frequency in obese patients. So, is there a correlation between OSA, MS and T2DM? OSA and MS has been defined as syndrome Z. Nora L. Nock, PhD; et al[9] worked on a project, the results of which demonstrate that sleep disturbance co-aggregates with other metabolic features to represent a single unifying trait, syndrome Z. Although their model awaits validation in other populations, it provides a tool for better understanding the synergistic risk of syndrome Z, compared with syndrome X, on type 2 diabetes and cardiovascular disease in future studies.

Hence in this study 134 patients having type 2 diabetes mellitus and satisfying the inclusion criteria were checked for OSA and Metabolic Syndrome.It was observed that : 48 patients (35.8%) were suffering from Metabolic Syndrome 66 patients (49.2%) were suffering from OSA out of which 32 (23.9%) had a high risk and 34 (25.4%) had a low risk. 37 patients (27.6%) were suffering from Syndrome Z. Thus, the prevalence of OSA as well as Syndrome Z was very high in our study. It was high compared to the findings by Surendra K. Sharma, et al[10] who conducted a study on 365 subjects. Out of these 365 subjects, 29.9% had Metabolic Syndrome, 6.8% had OSA and 19.9% had Syndrome Z.

Sharma SK, et al[1] conducted a door-to-door survey on 2860 subjects. Of these 2860 subjects, 43% were found to be suffering from metabolic syndrome and only 4.5% had syndrome Z. The high prevalence of syndrome Z in our study can be attributed to the smaller sample size as compared to the other studies mentioned above. As this was a hospital based study most of the patients were attending the hospital since long duration and were having advanced Diabetes with complications and might have added to our positive findings.

The mean age of the patients suffering from Syndrome Z was 58.32 ± 9.35 years. It was higher compared to other studies, where it was 47 years. We observed that as the age increased, prevalence of Syndrome Z increased. This can be explained by the fact that most of the subjects with Diabetes were older having longer duration of diabetes. Among the 37 patients suffering from syndrome Z, 48.6% were males and 51.4% were females, the M: F ratio being 1: 1.06. There was a slight female preponderance as reported by Alvah R. Cass, MD, SM; et al[11] but statistically insignificant.

In our study, cardio metabolic risk factors were similar in both groups except for Hypertension and positive family history of Coronary artery disease (CAD). Hypertension and family history of Coronary Artery Disease were significant risk factors for syndrome Z on univariate analysis. On multivariate analysis Hypertension was found to be an independent risk factor for Syndrome Z. In a cross-sectional study of men referred for diagnostic polysomnography, most of whom were subsequently shown to have OSA, Grunstein *et al*[12] showed that the severity of sleep disordered breathing (expressed as respiratory disturbance index, RDI) was an independent predictor of both morning systolic and diastolic blood pressure[13]. Many studies have reported a high incidence of cardiovascular events in patients having OSA. Syndrome Z can also be considered as a marker for future cardiovascular events in Diabetic patients. Cerebrovascular events (CVE) were slightly higher in syndrome Z patients (5.4%) than in subjects without syndrome Z (1.8%).Peripheral vascular diseases were found only in syndrome Z patients (5.4%) with no incidences in the opposite group. However, the occurrence of CAD in the former group of patients was significantly high. These findings were similar to those reported in previous studies validating OSA as a marker CAD.

The mean duration of diabetes was 9.63 ± 3.92 years in patients having syndrome Z, while it was 4.42 ± 2.33 years for those patients not having syndrome Z. This was significantly higher in syndrome Z patients (p value < 0.001). Larger number of syndrome Z patients had noncompliance (29.7%), while only 14% of the subjects not having syndrome Z were

noncompliant. Alvah R. Cass, MD, SM; et al[11] conducted a study on 297 adult participants who all were type 2 diabetics. According to their study, mean duration of diabetes was found to less i.e. 7.9 ± 6.4 years in patients with prior diagnosis of OSA as compared to that in patients with no prior diagnosis of OSA i.e. 10.4 ± 8. 7 years. However, this difference was found to be statistically insignificant.

Hermans et al in their study on OSA in DM found mean age as 66 ± 12 years, diabetes duration 15 ± 9 years, sleep apnea prevalence 8.2% and metabolic syndrome 86%. There were no differences in age, diabetes duration, education, smoking and blood pressure between groups. Their study included only female patients[14].

In our study, mean height of the subjects having syndrome Z was slightly lower i.e. 156.91 ± 9.04 cm as compared to that in subjects not having syndrome Z i.e. 158.22 ± 10.83 cm. Mean weight, Mean BMI and mean waist circumference of both males and females was significantly higher in syndrome Z patients than in the counter group. The results are in agreement with previous studies by Surendra K. Sharma, Vishnubhatla Sreenivas et al[10] and Alvah R. Cass, MD, SM; et al[11]. This again indicates that obesity, Metabolic syndrome and obstructive sleep apnea are a spectrum of abnormal morphological and physiological characteristics clustering in a diabetic patient.

In our study, all the biochemical parameters i.e., Fasting and post meal blood sugar levels, triglycerides were higher in syndrome Z patients and HDL levels are slightly lower in syndrome Z patients. But the difference was statistically significant for TG levels only. Pillai A et al[15] conducted an observational cross-sectional study of 52 consecutive patients attending the diabetes obesity clinic and reported prevalence of OSA in this clinical cohort as 58%. After adjusting for age, gender, body mass index, duration of diabetes, and insulin dose, increased severity of OSA was associated with increased HbA1c levels ($P<0.014$ for linear trend). We had not done HbA1c levels. We assessed the glycemic control by fasting and post meal blood glucose levels, which do not determine the long-term diabetes control. Syndrome Z may predict a more severe cardiovascular risk in T2DM as compared to MS or OSA alone.

Conclusion :

The prevalence of Syndrome Z i.e. Metabolic Syndrome and Obstructive Sleep Apnea is very high in Type2 Diabetes Mellitus. It was 27.6% in our study. Syndrome Z occurs in older diabetics with a female preponderance, increases with advancing age and duration of Diabetes and noncompliance to treatment. Hypertension is an independent risk factor associated with Syndrome Z. Syndrome Z has a positive correlation with the important parameters of Metabolic syndrome i.e. Hypertriglyceridemia and increased waist circumference. Syndrome Z has a positive correlation with obesity as determined by BMI. As BMI increases, prevalence of Syndrome Z increases.

Thus, screening diabetic patients for syndrome Z can have important therapeutic and prognostic implications for future cardiovascular events. Berlin questionnaire can be used as a screening tool for OSA.

Study Limitations :

A smaller sample size and short duration of study. Polysomnography was not conducted in all patients due to technical problems, because of which some patients might have been over-diagnosed for OSA.

Compliance with Ethical Standards :

Funding : This study was funded by ICMR STS and Support from Institute

Conflict of Interest : No conflict of interest declared by any of the authors

Ethical approval : All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional ethics committee.

Informed consent : Informed consent was obtained from all individual participants included in the study.

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