Clustering of Metabolic Syndrome and Obstructive Sleep Apnoea - Syndrome Z among Adult Nigerians with Systemic Hypertension: Prevalence and Clinical Correlates

Adeseye Abiodun Akintunde\textsuperscript{a,b} and Oladimeji George Opadijo\textsuperscript{a}

Abstract

Obstructive sleep apnoea (OSA) syndrome and metabolic syndrome are independent cardiovascular risk factors. Syndrome Z is the clustering of metabolic syndrome and obstructive sleep apnoea. Syndrome Z is associated with a higher cardiovascular risk profile compared to those without it. We aimed to determine the prevalence of syndrome Z among treated hypertensive subjects in a Nigerian hypertension clinic.

Methods: One hundred and four hypertensive subjects were recruited in this cross sectional study. Risk for OSA was defined according to the American Medical Association criteria while metabolic syndrome was defined according to the NCEP ATP III criteria. Echocardiography was performed on all hypertensive subjects. Fasting serum lipid and blood glucose were also performed after at least 8 hours. Statistical analysis was done using SPSS 17.0.

Results: The mean age of hypertensive subjects was 58.4 ± 11.8 years and consisted of 43.4% males. OSA was present in 52 (50.0%) while metabolic syndrome was diagnosed in 25 (24.03%) of hypertensive subjects. Syndrome Z was present in 21 (20.2%). Hypertensive subjects with syndrome Z had significantly higher left ventricular chamber wall dimension, fasting blood sugar, triglycerides and left ventricular mass than those without it. Mean transmural E/A ratio was significantly lower among hypertensive’s with syndrome Z compared to those without syndrome Z. Snoring and obesity were associated with increased risk for diagnosing syndrome Z (Odds ratio for syndrome Z were 12.67 and 1.53 respectively).

Conclusion: Clustering of metabolic syndrome and obstructive sleep apnoea syndrome is high among hypertensive subjects. We recommend that hypertensive subjects be screened for increased risk for OSA and metabolic syndrome to identify potential high risk subjects.

Keywords: Syndrome Z; Metabolic syndrome; Hypertension; Clinical correlates; Nigeria

Introduction

Hypertension is the commonest risk factor in Nigeria and it often coexists with multiple cardiovascular risk factors [1-3]. The cardiovascular risk of hypertensive subjects is therefore not only related to the level of blood pressure alone but on the presence of clusters of other cardiovascular risk factors [4,5]. This pattern of influence may be additive or multiplicative of individual CV risk factors present with possible modification by genetic and environmental influences [6]. Metabolic syndrome is constellation of cardiovascular risk factors such as elevated blood pressure, dyslipidaemia (hypertriglyceridaemia, low levels of high density lipoprotein cholesterol), hyperglycemia, and central obesity [6,7]. The primary underlying pathogenesis has been suggested to insulin resistance, obesity and inflammation [8]. The clustering of cardiovascular risk factors is associated with increased risk of development of cardiovascular disease (CVD) such as coronary heart disease (CHD) and stroke as well as increase in all-cause mortality [9,10]. It has been shown by various studies that the presence of multiple risk factors confers greater risk than a single risk factor [9-12].

Obstructive sleep apnoea is commonly under diagnosed but their associations with cardiovascular risk factors have been shown [13]. Observational and experimental evidence suggests that obstructive sleep apnoea may contribute to the development of systemic hypertension, cardiovascular disease, and abnormalities in glucose metabolism [14,15]. Syndrome Z is recently defined and involves the coexistence of OSA and metabolic syndrome. The morbidity and mortality associated with syndrome Z is rather multiplicative rather than additive of the constituent cardiovascular risk factors [16]. The additional heath benefit of identifying subjects with syndrome Z should lead to coordinated and integrated cardiovascular care among affected subjects in order to reduce their cardiovascular risk. Reports on syndrome Z is rare in this environment.

The aim of this study was to determine the prevalence of syndrome Z among treated hypertensive Nigerians and to describe their associated clinical correlates.

Materials and Methods

This was a cross sectional study done at the Cardiology unit of the Ladoke Akintola University Teaching Hospital, Osogbo, Osun State Nigeria. The study consisted of one hundred and four hypertensive patients being managed for hypertension who were recruited consecutively for this study after informed consent. Hypertension was diagnosed by either a persistent blood pressure >140/90 mmHg or the use of antihypertensive medications. History and clinical examination were performed. A structured data form was used to collect the data. Demographic variables such as age, body weight in kilograms, height in meters, waist circumference, hip circumference and gender of each participant were documented. Institutional Ethical Review Board gave ethical approval for the study.

The Epworth Sleepiness Scale (ESS) was used to determine excessive day time sleepiness. It is an eight item self administered questionnaire. Possible score ranges were from 0 to 24. For this study,
an ESS score of more than 11 was taken to mean excessive day time sleepiness EDS. The Berlin Questionnaire was used to identify the risk of having clinical obstructive sleep apnea. The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into high risk or low risk based on their responses to the individual items and their overall scores in the symptom categories. Subjects were categorized as high risk for having OSA if there were 2 or more categories where the scores were positive and low risk if there was only 1 or no category where the score was positive [17]. The Berlin questionnaire has been documented to be clinically sensitive and correlates significantly with the presence of OSA among various populations. Clinically Suspected Obstructive Sleep Apneas (CSOSA) was defined in accordance with the 2001 International Classification of Sleep Disorders [18].

The National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria was used to define metabolic syndrome [19]. This include

- Fasting serum glucose 6.1 mmol/l or on oral blood glucose lowering drugs,
- Blood pressure >130/85 mm Hg or on antihypertensive drugs,
- HDL cholesterol less than 1.04 mmol/l (in men) and <1.29 mmol/l (in women) or on lipid lowering agents,
- Serum triglycerides >1.7 mmol/l or on triglyceride lowering agents and
- Waist circumference >102 cm in men and >88 cm in women.

The presence of three of the five criteria qualifies for the diagnosis of metabolic syndrome. We obtained fasting glucose and lipid profiles among study participants using standard methods.

Echocardiography was performed on all the subjects using a SUI Spotlight Ultrasound with 3.5 MHz probe. 2-D, Colour and pulse wave Doppler were done. Echocardiography was done according to the recommendation of American Society of Echocardiography guidelines [20]. Basic measurements of LV systolic and diastolic dimension including posterior wall thickness, interventricular septum, and chamber dimensions were measured using M-mode echocardiography. Averages of three measurements were taken. LVM was calculated from the measurements of the left ventricle (LV) using the equation:

\[ \text{LVM (g)} = 0.81 \times [1.04 \text{ (interventricular septal thickness + posterior wall Thickness + LV end diastolic internal dimension)}] + 0.6 \times 21 \]

LVM index (LVMI) was calculated as LVM/height in meters 2.7. Correcting LVM for height 2.7 has been shown to minimize the effect of gender, race, age, and obesity on the validity of various parameters for the diagnosis of left ventricular hypertrophy for which many parameters exist [22,23]. Basic demographic parameters including age, weight body mass indices were taken. Statistical analysis was done using the Statistical Package for Social Sciences SPSS 17.0 (Chicago Ill.). Numerical data were summarized using means and standard deviation while categorical data were summarized using frequencies and percentages. Comparison between groups was done using student’s-test and Chi square as appropriate.

### Results

The mean age for the study participants was 58.4 ± 11.82 years. It consisted of 41 males (39.4%). The demographic and laboratory parameters are as shown in table 1. The frequency of occurrence of metabolic syndrome was 24.03% while the frequency of syndrome Z was 20.2%. Hypertensive subjects with syndrome Z were significantly older than hypertensive’s without syndrome Z as shown in table 2. Systolic blood pressure was higher, albeit not significant among hypertensive subjects with syndrome Z. Mean fasting blood sugar, mean fasting serum triglycerides, mean left ventricular posterior wall thickness in diastole, mean interventricular septal thickness in diastole, left ventricular mass and left ventricular mass index were significantly higher among hypertensives with syndrome Z compared to those without it. Mean high density lipoprotein cholesterol (HDL),

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>33.00</td>
<td>88.00</td>
<td>58.4</td>
<td>11.82</td>
</tr>
</tbody>
</table>

**Table 1:** Clinical and laboratory characteristics of study participants.

### Table 2: Clinical, laboratory and echocardiographic variables between hypertensives with syndrome Z compared to those without syndrome Z.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensives with syndrome Z (88)</th>
<th>Hypertensives without syndrome Z (21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.3 ± 12.6</td>
<td>57.8 ± 12.1</td>
<td>0.0368*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140.3 ± 14.4</td>
<td>134.7 ± 11.9</td>
<td>0.285</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.0 ± 10.8</td>
<td>83.8 ± 11.6</td>
<td>0.860</td>
</tr>
<tr>
<td>FBS (mmol/l)</td>
<td>6.0 ± 0.58</td>
<td>4.73 ± 0.81</td>
<td>0.000**</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.01 ± 0.8</td>
<td>0.73 ± 0.27</td>
<td>0.0109*</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>0.99 ± 0.13</td>
<td>1.00 ± 0.62</td>
<td>0.941</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>12.5 ± 2.1</td>
<td>10.8 ± 1.9</td>
<td>0.0307*</td>
</tr>
<tr>
<td>IVDs (mm)</td>
<td>14.0 ± 0.34</td>
<td>12.4 ± 2.5</td>
<td>0.0390*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>74.5 ± 16.3</td>
<td>66.8 ± 17.8</td>
<td>0.575</td>
</tr>
<tr>
<td>E/A</td>
<td>0.65 ± 0.21</td>
<td>1.1 ± 0.42</td>
<td>0.0179*</td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>59.5 ± 15.8</td>
<td>52.5 ± 16.7</td>
<td>0.0486*</td>
</tr>
</tbody>
</table>

Key to table: SBP-systolic blood pressure, DBP-diastolic blood pressure, FBS-fasting blood sugar, TG-triglyceride, HDL- high density lipoprotein, PWTd-posterior wall thickness in diastole, IVDs-interventricular septal thickness in diastole, EF-ejection fraction, E/A – ratio of early transmitial to late transmitial velocity, LVM-left ventricular mass, LVMI- left ventricular mass index.
diastolic blood pressure and ejection fraction were similar between the two groups (Table 2).

The odd ratios for developing syndrome Z are as shown in table 3. Epworth sleepiness scale score >11, high risk for OSA, obesity and presence of snoring are associated with increased odds for the presence of syndrome Z among hypertensive subjects.

Discussion

This study revealed that the prevalence of syndrome Z (clustering of metabolic syndrome and obstructive sleep apnoea syndrome) is high among Nigerians with hypertension. This pattern is almost similar to the distribution of metabolic syndrome among hypertensive subjects. Therefore hypertensives with OSA are almost likely to have metabolic syndrome with consequent increase in cardiovascular morbidity and mortality. Almost one fifth of the study participants were diagnosed to have syndrome Z in comparison with about one-fourth of hypertensive subjects with metabolic syndrome. The identification of subjects with increased CV risk for possible integrated and intensive cardiovascular care is a possible way of reducing CV risk in the population.

Clustering of CV risk factors termed metabolic syndrome was recognized as early as 1920 and it is related to insulin resistance and hyperinsulinaemia. Other features of MS include microalbuminuria, hypercoagulability, inflammation, hyperadrenergic drive and endothelial dysfunction [24].

OSA is frequently under diagnosed in this environment. Adegove et al. [25] reported that the prevalence is high among the population. Each constituent CV risk factor in syndrome Z contributes to the total CV risk profile. Therefore, it is important to treat each of them in order to further reduce the CV risk of that population. Hypertensive subjects with syndrome Z was shown in this study to have a higher left ventricular mass, left ventricular wall dimension than hypertensive subjects without syndrome Z. The higher fasting blood sugar, left ventricular mass, triglycerides and cholesterol further suggest the higher cardiovascular risk of hypertensive subjects with syndrome Z in agreement with similar studies [16,26].

This study also suggests that the metabolic syndrome may be a marker of OSA. This is in agreement with the study by Lam et al. among Hong Kong Adults [26]. The prevalence of syndrome Z and metabolic syndrome are similar in pattern and associated with similar clinical correlates such as increased fasting blood sugar, left ventricular mass, significantly higher left ventricular chamber wall dimension and diastolic dysfunction compared to hypertensive subjects without metabolic syndrome and/or syndrome Z there is now evidence of independent associations of OSA with systemic hypertension, insulin resistance, ischemic heart disease and stroke [27,28].

Syndrome Z was introduced in medical literature by Ian Wilcox in 1961. The importance of identifying this syndrome is for risk factor modification and to inculcate OSA which is known to increase cardiovascular risk into routine CV screening [29]. There is very little information about the epidemiology of syndrome Z among Africans. Therefore this study provides the first set of information on syndrome Z among hypertensive subjects. OSA and Metabolic syndrome share a common pathogenetic mechanism with consequent increased CV risk. Effective management of OSA with Continuous Positive Airway Pressure has been shown to reduce the CV risk associated with OSA while treating individual cardiovascular risk definitely reduced the CV risk associated with metabolic syndrome [16,28]. Therefore, hypertensive subjects with syndrome Z may be at a much higher cardiovascular risk than the present of either metabolic syndrome or OSA in isolation among hypertensive subjects [15,16].

In conclusion, this study suggests that hypertensive subjects with metabolic syndrome should be screened for increased risk for OSA. It also shows that the prevalence of syndrome Z is significantly high among hypertensive subjects in Nigeria.

References

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