REVIEW ARTICLE

Syndrome Z – Current Status

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Syndrome Z is a combination of metabolic syndrome (Syndrome X) and obstructive sleep apnoea (OSA) as highlighted by Ian Wilcox (1). Metabolic syndrome (MS) itself is a constellation of obesity, insulin resistance, hypertension and dyslipidemia. On the basis of National Cholesterol Education Programme ATP (III) definition, Third National Health and Nutritional Examination Survey (NHANES) estimated the age adjusted prevalence of MS in USA to be an astounding 23.7%. It came into vogue in the 1920's with reference to the clustering of hypertension, hyperglycemia and gout. The definition of MS has undergone several modifications over time. (2,3) Subsequently many features have been reported to be associated with MS viz. proinflammatory state, prothrombotic state, hyperleptinemia, hypoadiponectinemia, hyperuricemia, endothelial dysfunction, microalbuminurea etc. (2).

According to the International Diabeties Federation's (IDF) definition (4), for a person to be defined as having the MS one must have Central Obesity (waist circumference ≥ 90 cm for Asian men and ≥ 80 cm for Asian women).

Plus

Any 2 of the other 4 components.

1. Raised triglyceride level ≥ 150 mg/dl or patient already on specific treatment for this lipid abnormality.
2. Reduced HDL cholesterol < 40 mg/dl in males and < 50 mg/dl in females or taking specific treatment for this lipid abnormality.
3. Raised blood pressure: Systolic ≥ 130 mg/dl or diastolic ≥ 85 mmHg or treatment of previously diagnosed hypertension.
4. Raised fasting plasma glucose ≥ 100 mg/dl or ongoing treatment of Diabeties mellitus (For many research studies a figure of ≥ 110 mg/dl is being used as the IDF's criteria appears rather stiff to many)

As has happened in the past, the defining criteria and these numbers could see a change in future also. It should not be a surprise if more components are added in future considering the complexity of this largely life style disease. Obstructive sleep apnoea has so firmly established itself as a part and parcel of the constellation of these disease components and its association so frequent that MS + OSA is now labeled as "Syndrome Z". And rightly so because there is a complex interplay between obesity, glucose intolerance, OSA, hypertension (HTN) and dyslipidemias. Many of these components are known to aggravate one another and it has even been proposed that OSA should be considered a metabolic disease (5). It is not just a story of repetitive upper airway obstruction, recurrent oxygen desaturation and arousals. The repercussions go far beyond. And we can't stop short at MS and OSA in the current and future research. What about sympathetic activation, endothelial dysfunction, oxidative stress, systemic inflammation and hypercoagulability? One day we may develop their definitive markers and add on to the existing numbers in the Syndrome Z. This field will continue to evolve and redefine itself but what we know for sure is its impact and load on the cardiovascular (CVS) & even cerebrovascular pathology. Since each component of Syndrome Z has significant effects on CVS and cerebrovascular system, it is important to treat each individual component diligently in order to reduce morbidity and mortality. There is ample evidence of independent associations of OSA with systemic HTN, Insulin resistance, CAD and stroke (6,11).

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Pathophysiology

In the pathogenesis of MS, insulin resistance and visceral obesity seem to be key factors. (3,12,13) The criteria defining metabolic syndrome include visceral obesity because studies have revealed that visceral fat provides a great amount of cytokines and hormones such as TNF-α, IL- 6 and leptin which may be associated with atherosclerosis. Insulin resistance is thought to play a part in pathogenesis but precise relationship is not defined. Visceral fat accumulation (VFA) correlates with the severity of OSA (14) and is a key factor for the development of MS (3,12,13)

In the abdominal CT scan a VFA > 100 cm^2 is a diagnostic feature of MS. (3,12,15) Obesity ,especially the presence of VFA could worsen metabolic abnormalities such as insulin resistance, while insulin resistance a putative background of MS, could be associated with OSA (11,16). There is a complex interplay as hypoxia leads to increased leptin levels which affects glucose uptake. Interestingly continuous positive airway pressure (CPAP) treatment improves insulin sensitivity within a few days before any possible changes in body weight or life style become apparent. OSA itself appears to predispose to insulin resistance. Increased production of TNF- α (17) and increased sympathetic drive (18,19)may partly explain changes of glucose homeostasis in OSA. A small number of studies, however do not support this (20,21,22).

OSA may contribute to HTN through increased sympathetic activation (18,19), leptin, aldosterone, fatty acids, oxidative stress and insulin resistance (23). CPAP alone reduces blood pressure in HTN patients with OSA independent of all other factors. The association between OSA and lipid metabolism is addressed in Wisconsin sleep health heart study (26). Factors such as genetic predisposition, physical inactivity, aging, inflammation and hormonal dysregulation are also implicated in pathogenesis of MS. Are not many of them related to OSA also?

OSA and alternation in glucose metabolism

MS was previously known as insulin resistance syndrome reflecting the important position of insulin resistance in MS (25). If OSA leads to insulin resistance which has been confirmed by numerous clinical and cross-sectional studies then it leads to other derangements also attributable to insulin resistance such as HTN, hypertriglyceridemia and visceral obesity. Thus OSA combined with MS meaning Syndrome Z may have multiplicative effect.

OSA, insulin resistance and MS are closely related to indices of obesity and central obesity including BMI, waist circumference and neck circumference (26). Obesity plays important role in development of OSA by mechanical loading in upper airways.

In its extreme form it also leads to heavy mechanical loading of the chest wall and abdomen (thereby the diaphragm) which initiates the process of hypoventilation and resetting of the respiratory control and CO_2 levels further causing hypoxia, sympathetic and oxidative stress starting another vicious cycle within a vicious cycle.

In the only longitudinal study that used polysomnography (PSG) to assess OSA, Reichmuth and colleagues (27) analyzed 1387 subjects in the Wisconsin study cohort. The author reposted that DM was prevalent in OSA independent of other risk factors at baseline.

Intervention studies with CPAP in patients with OSA and hyperglycemia have considerable disagreement on outcome. The study population and techniques used to assess glucose metabolism have been variable. The treatment period with CPAP ranged from 1 night to 6 months. A proper larger and longer controlled clinical trial is needed to give a more definitive direction.

Syndrome Z and inflammation

It has been proposed that repetitive episodes of intermittent hypoxia followed by reoxygenation as seen in OSA simulates ischaemia-reperfusion injury which may result in generation of reactive oxygen specimens (ROS). ROS can upregulate transcription factors that control inflammatory pathways like NFkB. This also modulates neurohumoral pathways, activate systemic inflammation as well as increase susceptibility to oxidative stress.

Abdominal obesity *per se* appears to induce a state of low grade inflammation with adipocytes and macrophages being sources of following proinflammatory mediators:

1. **Cytokines:** TNF α and IL-6 produced by macrophages and adipocytes induce insulin resistance and are also postulated to be mediators of sleepiness and fatigue. They are increased in OSA patients

(28,29) and reduce with CPAP treatment (29,30).

2. **NFkB:** It is the master switch in the transcription of numerous genes involved in inflammatory pathways. It is involved in pathgenesis of MS and atherosclerosis. Circulating neutrophils and monocytes showed elevated NFkB building activity in OSA patients which reversed with CPAP.
3. **CRP:** It is a biomarker of inflammation and is used in risk stratification of cardiovascular disease (CVD). Its levels increase with increasing number of components of MS. Data on relationship of OSA and CRP have been conflicting.
4. **Leptin and Adiponectin:** They are fat derived hormones. Leptin regulates energy and has respiratory stimulant effect and an effect on vasculature.
5. **Leukocyte adhesion, platelet activation and other prothrombolic activity:** MS and OSA are associated with elevated circulating levels of soluble cell adhesion molecules which decrease with CPAP treatment (31,33). Activated leukocytes express cell adhesion molecules that mediate interaction with the endothelium intiating vascular inflammation. OSA patients have raised fibrinogen and prothrombin activator inhibitor – 1 (PAI-1) which are prothrombotic and also raised in MS.

OSA and cardiovascular system

Pathophysiologic mechanisms that are present in patients with OSA including sympathetic activation, endothelial dysfunction, oxidative stress, systemic inflammation, hypercoagulability, hyperleptinemia and insulin resistance may influence the development and progression of cardiac and vascular pathology. Patients with OSA have abnormalities in each of the core components of MS. Since most of these mechanisms are independently present in MS it can be our informed opinion that these effects in Syndrome Z are atleast additive though there could be a synergistic role of various viscous cycles initiated by MS and OSA within syndrome Z.

Observational studies have suggested strong association of OSA with systemic HTN, heart failure, arrhythmias and pulmonary hypertension (PHT). Acute cardiovascular (CV) stressors include recurrent hypoxemia with reoxygenation, cyclic tachybradyarrhythmia, recurrent swings in intrathoracic pressure and central nervous system arousals. CV homeostatic mechanisms are disrupted as demonstrated by daytime abnormalities in sympathetic nervous system (SNS) function and heart rate variability. There is increased chemo-reflex response to hypoxemia. Lung inflation serves to homeostatically maintain autonomic balance but is incomplete due to recurrent apnoea and hypopnoea during 1/3rd of our life that we spend sleeping. Re-oxygenation promotes oxidative stress by formation of ROS and leads to inflammation and mitochondrial dysfunction. Intrathoracic pressure swings during effort against obstructed upper airways is associated with acute changes in pulmonary artery pressure (PAP), blood flow and increased cardiac afterload. Enhanced venous return can result in acute leftward shift of interventricular septum and alterations in transmural cardiac pressures with an impedence to left ventricular filling and increase in myocardial oxygen demand. Also CNS arousals due to OSA result in abrupt increases in sympathetic tone, HR and BP. Let us not forget that all these changes occur when the SaO_2 is low, at times very low in OSA.

OSA leads to rise in BP during sleep. Also evidence is mounting for its role in diurnal HTN. Dipping phenomenon (10-15% fall in BP during sleep) is lost in OSA patients while CPAP improves BP in these patients. Rise in BP correlates with high level of Apnoea-Hypopnoeas Index (AHI) and sleep time below 90% SaO_2. Regarding cardiac arrhythmias, sleep heart health study (SHHS) (34) showed that severe OSA (AHI>30) had a higher rate of atrial fibrillation (AF), non-sustained ventricular tachycardia and ectopic ventricular beats. Bradyarrhythmias are also encountered in OSA while cyclic tachybradyarrhythmia is invariably present in OSA. Seventy five percent of episodes of persistent AF in patients with OSA occurred in night hours (8PM-8AM). Nocturnal hypoxemia is implicated for that.

Heart failure in OSA and indeed syndrome Z can be attributed to many factors viz higher BP, significant oxygen desaturation, increased BMI, diastolic dysfunction, increase in afterload, incidental AF and probably systolic LV dysfunction. Studies from Kenko and colleagues (35) and Mansfield and colleagues (36) have shown improvement in LV ejection fraction with CPAP.

OSA and indeed syndrome Z also lead to hypoxic pulmonary vasoconstriction which is critical autoregulating mechanism in maintaining appropriate ventilation-perfusion relationship. Repeated vasoconstriction leads to pulmonary vascular remodeling.

Syndrome Z and stroke

Artz and colleagues in Wisconsin sleep cohort demonstrated that pre-existing sleep disorder may be a risk factor for incidence of stroke. Stroke itself may lead to OSA, central sleep apnoea, Cheyne-Stokes breathing and complex sleep apnoea by disruption of central respiratory control mechanism or brainstem mediated upper airway reflexes. Seventy percent of patients with acute stroke or TIA had AHI > 10 (37). Other components of syndrome Z viz hypertension, dyslipidemias, high fasting glucose and obesity have already proved their contributation in increasing the risk of stroke.

OSA and newer cardiovascular diagnostics:

Components of MS have a proven role as major CV risk factors. OSA also leads to increased interventricular septal thickness, diastolic dysfunction, and in its more severe form it can lead to diastolic heart failure (DHF). Echocardiogram can confirm IVS thickness, prolonged IVRT (Inter ventricular relaxation time) and decreased E/A ratio. IVRT is the time interval from closing of aortic valve to the opening of mitral valve. Prolonged IVRT suggests delayed relaxation of LV due to thickening and stiffening of its walls. Decreased E/A means slower filling of LV during diastole allowing left atrial contraction to play a dominant role in pushing blood into LV. Both prolonged IVRT and decreased E/A signify diastolic dysfunction and in its severe form can lead to diastolic heart failure (DHF). Severe OSA was noted in 55% of patients with DHF. Diastolic dysfunction is common in OSA of varying severity (36.8%). OSA patients with diastolic dysfunction were older, with a higher prevalence of HTN and associated with more severe SO_2 drop during sleep. IVRT correlated with AHI. Studies have been controversial regarding OSA leading to LV wall thickness. CPAP can improve LV systolic and diastolic function. OSA and Cheyne-Stokes respiration with central sleep apnoea (CSR-CSA) can co-exist in patients with CHF. CSR-CSA is a consequence rather than a cause and is associated with increased mortality. Newer work on spectrographic analysis of cardiopulmonary coupling has shown that CPAP has a very variable response in CSR-CSA and complex sleep apnoea patients. A combination of CPAP, oxygen and CO_2 rebreathing is ideal.

Recent developments like carotid intima media thickness (CIMT) and brachial artery flow mediated dilatation (BAFMD) has allowed assessment of earliest signs of vascular damage in simple reliable and reproducible manner with low cost and without the hazard of radiation exposure. All these techniques are basically aimed at diagnosing atherosclerotic changes and cardiac vascular risk at an early stage in patients with syndrome Z.

Conclusion

The controversies regarding the exact relationship between OSA and MS are being demystified giving birth to syndrome Z. However, majority of cross-sectional studies lack adequate size or rigorous control for comfounding factors in particular visceral obesity. Both OSA and MS and their outcomes regardless of whether they are independent, additive or synergistic, are well established to be modifiable by life style measures and other more interventional therapies. Logic dictates that the presence of multiple vicious cycles within MS and OSA should favour a synergistic effect but it remains to be proved. The prevalence of this life style disease and ever increasing incidence of MS and OSA individually and in the form of syndrome Z world wide has attained such enormous importance that if collective effort of physician community, media, government agencies and NGOs fail, then this scourge will take millions of lives – it is a slow killer.

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