Review Article

Chronic obstructive pulmonary disease and the metabolic syndrome: Consequences of a dual threat

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ABSTRACT

The metabolic syndrome is found to be more frequent in chronic obstructive pulmonary disease (COPD). The presence of inflammatory markers in circulation, sputum, and broncho-alveolar fluid suggest systemic inflammation is one of the potential mechanisms responsible for both COPD and metabolic syndrome. Physical inactivity, skeletal muscle dysfunction, hypogonadism, and steroid use are also important causes of the metabolic syndrome in COPD. Obesity and insulin resistance is found to be more common in mild to moderate stages (I and II) of COPD. Patients with COPD and the metabolic syndrome have increase risk of morbidity and mortality due to cardiovascular disease. This review describes in details the various components of metabolic syndrome and its impact on long outcomes in COPD patients.

Key words: Chronic obstructive pulmonary disease, metabolic syndrome, physical inactivity, systemic inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is a growing epidemic and remains a major public health problem.[1-3] The overall prevalence of COPD is estimated to be in the vicinity of 4-5% in our country.[4,5] COPD has been associated with several extra-pulmonary systemic manifestations inclusive of diabetes mellitus, osteoporosis, and metabolic syndrome.[6,7] Several etio-pathogenic mechanisms have been proposed as a possible link between COPD and metabolic disorders that include systemic inflammation, adipose tissue inflammation, and physical inactivity.[8-10] This review focuses on the dual threat presented by the metabolic syndrome and its associated abnormalities in patients with COPD.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.139212

Chronic Obstructive Pulmonary Disease

COPD has been widely recognized as a major cause of morbidity worldwide and is likely to be the third leading cause of death by the year 2020.[11] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is defined as a preventable and treatable disease with major extra-pulmonary effects. The Global Initiative for Lung Disease (GOLD) has classified COPD into four stages depending upon the spirometric findings and the severity of symptoms.[12]

Clinical features and systemic manifestations of COPD

The combination of symptoms such as cough, sputum production, and progressive exertional breathlessness are frequent in COPD. Over the last couple of decades, there has been a fair deed of published data on the extra pulmonary manifestations of COPD.[13-15] The consensus statement of GOLD has also defined COPD as a disease with significant extra pulmonary manifestations.

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COPD has several systemic manifestations and the details are listed in Table 2

Metabolic abnormalities like type 2 diabetes mellitus, obesity and the metabolic syndrome (MetS) are common in COPD.[16] Obesity is seen in approximately 18% of patients with COPD and is far more common in the early stage (stage - I and stage - II).[17]

Co-existence of COPD and Metabolic syndrome (MetS)

By 2016 it is estimated that about 59.1 lakh people in urban areas and 163 lakh people in rural areas in India will suffer from COPD.[18] The prevalence of obesity and metabolic syndrome is rapidly increasing in India and approximately about one-third of the urban populations have MetS.[19]

Metabolic syndrome is found to be twice more common in COPD when compared to the general population. Several studies from different parts of the world have shown a prevalence of 25.6-60.9%.[20-23] A study by Funakoshi *et al.* on 7189 Japanese males aged 45-88 years found that patients with GOLD staging II - IV have a high probability of having co-existent MetS with an Odds ratio (OR) of 1.33. Among the various components of MetS, waist circumference (OR, 1.76; 95% CI, 1.24-2.50) and blood pressure (OR, 1.37; 95% CI, 1.08-1.74) showed a significant association with airflow obstruction of GOLD stage II-IV.[20] In a German study of 170 patients with COPD and 30 patients with chronic bronchitis, the frequency of MetS were found to be 53%, 50%, 37%, and 44% in GOLD stage I, II, II and IV, respectively (average, 47.5%). They had observed a slightly lower frequency of MetS, central obesity, and lipid abnormalities among patients with severe to very severe COPD.[23]

COPD and Individual Components of the Metabolic Syndrome

COPD and Obesity

The relationship between COPD and obesity is being increasingly recognized; however, the association is still poorly understood. In a study conducted in Madrid which included 198,670 patients with age above 40 years, about 3.2% of the subjects were detected to have COPD among which 20% had diabetes, 25% were obese, and 34% had dyslipidemia.[24] Steuten *et al.* conducted a study to look at the association of severity of COPD and BMI among 317 subjects in the Netherlands. The overall prevalence of obesity was 18% with the highest prevalence being in subjects with mild to moderate COPD (stages 1 and 2). The prevalence was 23.5% in stage-2, 16.1% in stage-1, and 5.9% in stage 4.[17] Obesity is known to have a significant impact on the respiratory function of subjects with or without COPD.[25,26] The effects of abdominal obesity on lung functions are as follows: (a) Abnormal ventilation/perfusion ratio, (b) Decreased chest wall and pulmonary compliance, (c) Increased work of breathing, (d) Reduction of ventilatory muscle strength and endurance, and (e) Small airway dysfunction and expiratory flow limitation [Table 1].[25-27]

In patients with COPD, obesity has an unusual impact that is commonly, referred as "Reverse Epidemiology of Obesity". A meta–analysis by Cao *et al.* analyzed data on 22 studies which included about 21,150 subjects. It was found that patients with a lower BMI had a higher mortality rate when compared with normal BMI subjects. Those subjects who were overweight and obese had a lower risk of mortality.[28] The relative risk for mortality is found to be decreased in overweight and obese patients with stages 3-4 while it increases in those with stage

Table 2: Systemic manifestations of COPD

Metabolic disorders
Type 2 diabetes mellitus
Metabolic syndrome
Dyslipidemia
Cachexia
Obesity
Skeletal muscle wasting
Bone diseases: Osteopenia and osteoporosis
Cardiovascular disease
Ischemic heart disease
Hypertension,
Pulmonary hypertension
Corpulmonale
Cancer: Lung cancer (small cell and non-small cell cancer)
Obstructive sleep apnea
Depression and anxiety disorders

COPD: Chronic obstructive pulmonary disease

Table 1: Classification of COPD as per GOLD criteria

GOLD stage	Severity	Symptoms	Spirometry
0	At risk	Chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	FEV_1/FVC <0.7 and FEV1 80% predicted
II	Moderate	With or without chronic cough or sputum production	FEV_1/FVC <0.7 and 50% FEV1<80% predicted
III	Severe	With or without chronic cough or sputum production	FEV_1/FVC <0.7 and 30% FEV1<50% predicted
IV	Very severe	With or without chronic cough or sputum production	FEV_1/FVC <0.7 and FEV1 <30% predicted or FEV_1<50% predicted with respiratory failure or signs of right heart failure

COPD: Chronic obstructive pulmonary disease; GOLD: Global initiative for chronic obstructive lung disease; FVC - Forced vital capacity; FEV1 - Forced expiratory volume in 1 second

1-2 disease; however, the exact mechanism has not yet been established.[29] The weight loss, muscle wasting and loss of fat free mass is more prominent in late stages 3 and 4 in COPD also known as Obesity Paradox.[30] Thus it indicates that both cachexia and obesity represent the two extremes of a spectrum of metabolic abnormalities that are seen in patients with COPD leading to adverse clinical outcomes.

COPD and body composition

Body composition has an important prognostic impact on the nutritional status of patients with COPD. Low BMI, particularly in the advanced stages is associated with an increase in all cause and COPD-related mortality.[31] Alteration in body composition can affect ventilatory function, exercise tolerance and skeletal muscle function. However, recent studies have shown that the Fat-free Mass (FFM) index is a much more important determinant.[32] Schols *et al.* have prospectively followed up 412 stable COPD (stage -3 and 4) subjects for 2-5 years or till the point of death whichever was earlier. The FFM was found to be a better predictor of mortality irrespective of FM (fat mass).[33]

COPD and lipoprotein metabolism

The pattern of dyslipdemia in COPD has not been well characterized. The CONSISTE study is a study to assess the cardiovascular risk factors in COPD subjects. COPD subjects had the highest prevalence of IHD (12.5% vs. 4.7%) when compared to controls. Dyslipidemia was found in 48.3% of COPD patients and 31.7% among controls.[34] A study in a tertiary care hospital in South India revealed that the mean LDL among COPD patients was 114.89 ± 19.61 (mg/dl) against the control group who had a mean LDL of 96.22 ± 19.96 (mg/dl) which was statistically significant ($P < 0.05$).[35]

The data on long term-effects of statins in COPD is limited. In the Rotterdam study the effect of statins was prospectively assessed in COPD patients over a period of more than 2 years. Statins are associated with a reduction in death rate by 36%.[36] Statins have many pleiotrophic effects such as anti-inflammatory and immunomodulatory properties. Statin therapy was associated with a 30% decrease in risk of COPD exacerbation.[37]

COPD and diabetes

The prevalence of diabetes in COPD is approximately about 3-12%.[38,39] Systemic inflammation is probably an important contributory factor responsible for both COPD and diabetes mellitus. The nurses' healthy study: a prospective study over an 8-year period had showed that COPD patients have a 1.8% relative risk of developing diabetes. The markers of inflammation such as IL-6, TNF-α, and CRP are elevated in both COPD and diabetes and these markers are elevated to a greater extent in overweight and obese COPD patients.[40] A study by Engstrom *et al.* described that reduced lung function is an important risk factor for the development of diabetes in COPD.[41] Mannino *et al.* shows that subjects with stage 3-4 had a higher risk for developing diabetes with an odds ratio of 1.5 (CI: 1.1-1.9).[6]

COPD and hypertension

The risk factors between COPD and CVD are quite common, inclusive of smoking. Coronary artery disease, hypertension, pulmonary hypertension, and heart failure are frequently occurring cardiovascular disorders amongst patients with COPD. A health survey conducted several years ago, 1992, from the USA, reported an incidence of hypertension 6.2% in COPD.[42] The incidence of hypertension can vary from 6-50% and depends upon the severity of airflow of obstruction.[43,44] A recent study (INDACO study) demonstrated a 53% incidence of hypertension.[44] The pathological mechanisms responsible for hypertension in COPD are hypoxia related vasoconstriction, free radical injury, endothelial dysfunction, and arterial stiffness.[45-47] Control of hypertension in COPD subjects can improve the cardiovascular-related mortality.[48,49]

Pathogenesis of Metabolic Syndrome in Copd

The pathogenesis of COPD and metabolic syndrome is multi-factorial in origin.[50,51] The risk factors for developing COPD and MetS are found to be similar in many ways. The important risk factors which linking the pathogenic mechanism between COPD and MetS are smoking, genetics, obesity, physical inactivity, and airflow limitation.[16,52] The D.E.S.I.R. study from France has shown that the MetS occurs more frequently among current smokers. The potential mechanism responsible for development of COPD and the MetS in a smoker is primarily due to systemic inflammatory response.[53] A recently published study from Italy had shown that MetS is more common in current smokers and pack per years and are found to have correlation with various parameters of MetS.[54]

Obesity and MetS are also relatively more common in restrictive lung disease. The Guangzhou Bio bank cohort study demonstrated that the risk of MetS is more common in those with significant airway obstruction.[55] This study also showed that central obesity is the main factor responsible for airflow obstruction in MetS. Several mechanisms has been proposed regarding the association between obesity and airflow limitation (a) decrease in

chest and lung compliance (b) small airway dysfunction and expiratory airflow limitation (c) variable reduction in ventilatory muscle strength and endurance (d) increased work of breathing.[25,26]

There are several pathogenic mechanisms that have been proposed to establish the link between COPD and MetS; however, they are still poorly understood. The proposed mechanisms are as follows:[50-52]

- Common pathophysiological mechanisms - systemic inflammation
- Adipose tissue inflammation
- Physical inactivity
- Hypogonadism
- The effect of steroids.

The risk factors associated between COPD and MetS are mediated primarily through low-grade inflammation. Low-grade inflammation has been described as the common pathway responsible for MetS and comorbidities in COPD. The pathogenic mechanisms linking risk factors and development of COPD and metabolic syndrome are shown in the Figure 1.[50]

Systemic inflammation as a common pathological mechanism

Fabbri *et al.* proposed COPD as a chronic inflammatory disorder.[56] It was initially thought that the markers of inflammation only increased in severe cases of COPD. However, subsequent studies have shown that circulatory inflammatory markers increases irrespective of lung function impairment.[57,58] Gang *et al.* reported a meta-analysis of 14 reports which confirmed a strong association between COPD and inflammatory markers such as CRP, fibrinogen, and TNF-α.[59] Various studies have shown a rise in the number of inflammatory markers like TNF-α, CRP, lipopolysaccharide-binding protein, lipid peroxidation products, and inflammatory cells in peripheral blood.[60-63] Pulmonary inflammatory biomarkers in induced sputum, bronchoalveolar lavage, endobronchial biopsy have also been studied to correlate the association between COPD and systemic manifestation.[64,65] Stefan Ropcke *et al.* studied 100 different inflammatory markers among 23 healthy smokers and in 24 smoker COPD patients. Markers associated with neutrophilic inflammation (MMP9, Elastase, Calprotectin, MMP9/TIMI1 ratio, IL-6, BAL neutrophils) and pro-inflammatory markers (IL-6, IL-β, IFN-α, I, MIG, and MIP-1α) are found to be significantly elevated.[66] The increase in circulating inflammatory markers in COPD has been considered as a part of the "spill over" of the inflammatory mediators from the pulmonary compartment which is primarily responsible for systemic inflammation. Figure 2 shows spill over hypothesis.[15] Therefore, it is suggested that systemic inflammation may probably be the common pathogenic mechanism responsible for genesis of COPD and its other comorbidities such as metabolic syndrome.[15,50] However, many studies refuted this

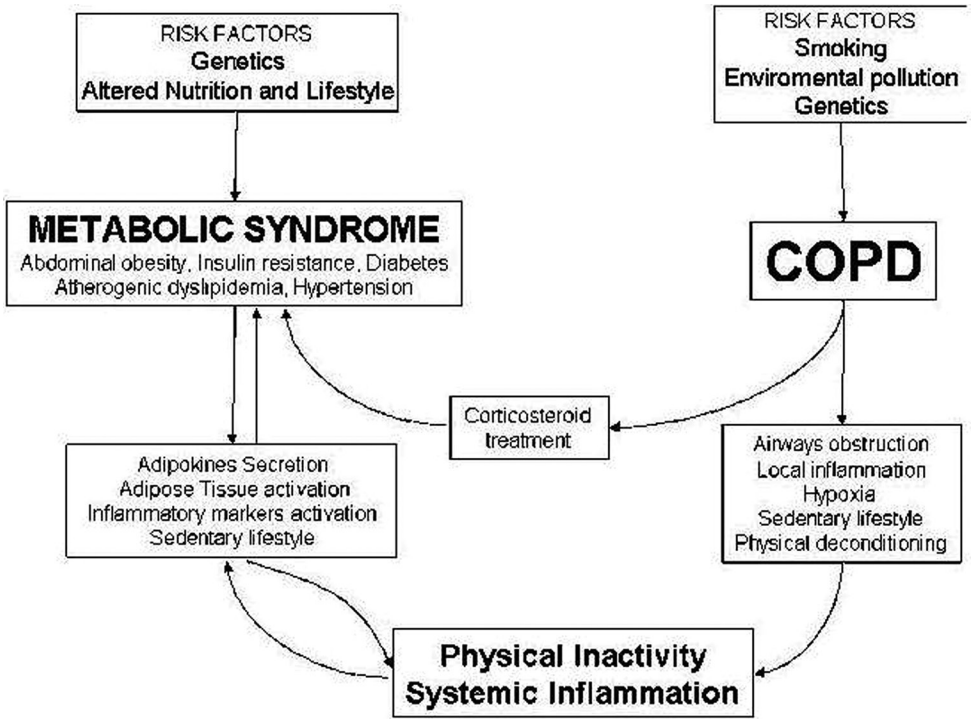

Figure 1: Pathogenic mechanism linking between the risks factors of COPD and metabolic syndrome. (Adapted from Clini *et al.* COPD and the metabolic syndrome: An intriguing association. Intern Emerg Med 2013;8:283-9.[50])

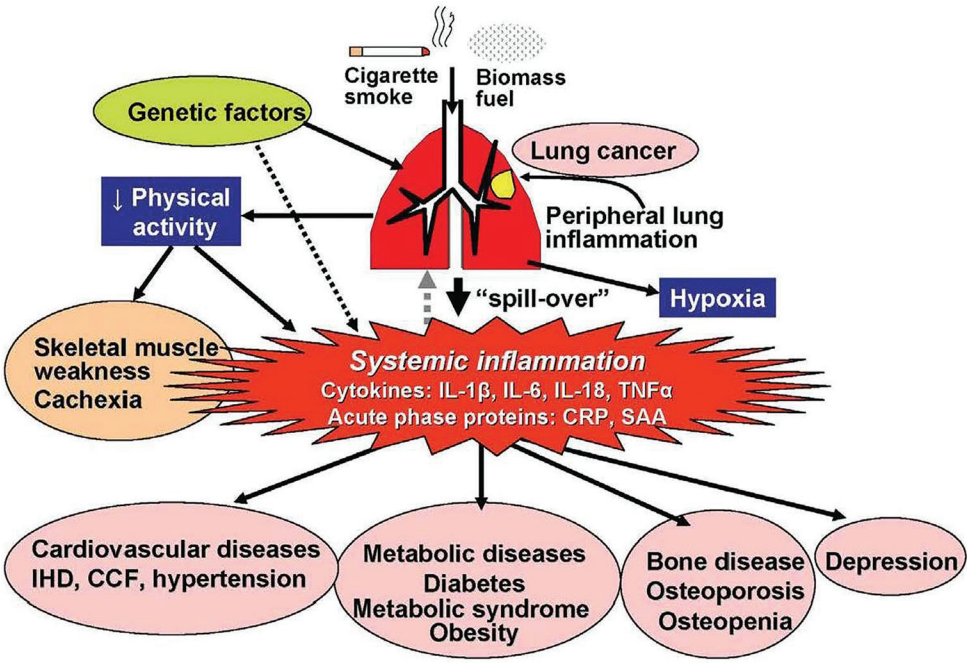

Figure 2: Systemic inflammation – spill over hypothesis. (In a patient with COPD there is a spillover of peripheral lung inflammation into systemic circulation which resulted in increased level of various inflammatory markers such as: IL-1β, IL-6, IL-8, and TNF-α. These systemic inflammatory markers are thus responsible for various complication associated with COPD such as; cardiovascular disease, hypertension, skeletal muscle weakness, etc. These systemic inflammatory markers are also responsible for the development of obesity, metabolic syndrome and diabetes in COPD patients. Adapted from Barnes PJ. Chronic obstructive pulmonary disease: Effects beyond the lungs. PLoS Med 2010;7:e1000220.[15])

hypothesis and suggested a possible alternate mechanism. The ECLIPSE study showed that the percentage of sputum neutrophils was poorly correlated with the severity of COPD and so there was no significant association with the severity of inflammation and the exacerbation rate of COPD.[67] Even intervention studies in COPD-like monoclonal antibodies against IL-8 and Anti-TNF-α antibodies -infliximab do not significantly modify the local or systemic inflammatory mediators. The role of the spill over hypothesis has been further emphasized in recent studies by studying the relationship between the various inflammatory biomarkers and pulmonary tissue-derived proteins such as surfactant D-derived proteins from pneumocyte -II.[68] A recent study by Kim *et al.* studied the candidate SNP of two pneumoproteins clara cell secretory protein (CC16) and surfactant protein D (SP-D) which appear to be strongly correlate with COPD.[69] However, the roles of such biomarkers are yet to be fully established.

Adipose tissue Inflammation

Adipose tissue inflammation (AIT) has been proposed to be one of the important contributors to systemic inflammation in obese COPD patients.[70,71] In obese COPD patients, adipose tissue inflammation is primarily related to relative adipose tissue hypoxia. There are several factors that are responsible for relative adipose tissue hypoxia a) reduction in the unit blood supply to adipose tissue mass, b) poor oxygenation of area with large adipocytes due to poor neo-vascularization and location away from the normal diffusion distance.[72,73] This results in relative adipocyte hypoxia and an increased inflammatory response. Inflammation of large adipocytes are associated with an increased production of pro-inflammatory adipokines IL-6, TNF-α, PAI-1 and leptins. Inflammation of adipose tissue has an adverse effect on insulin signaling pathways. Relationships have been observed between high adiposity, insulin resistance and the adipose tissue expression of macrophage cell surface receptor CD68.[71] AIT is manifested by an increase in CD68 and TNF-α expression that plays an important role in the whole-body insulin resistance of patients with COPD.[74]

Hypogonadism/low testosterone levels in COPD

The prevalence of hypogonadism is about 22-69% in COPD. The potential causes of hypogonadism in COPD are hypoxemia, hypercapnia, and glucocorticoid therapy.[75] Systemic inflammation has also been described as an important cause of hypogonadism.[76] The ECLIPSE study included 1296 male subjects of stages – II to IV COPD who were prospectively followed for 3 years without any intervention. The median testosterone level was 439 ng/ml and the level was correlated with a higher body mass index (Spearman's r = -0.47).[77] Similarly Laghi *et al.* showed that BMI was higher in hypogonadal COPD patients when compared with eugonadal men of same age.[78] Low testosterone levels are associated with diminished

energy levels, libido, bone mass, and muscle mass.[79] The association between hypogonadism and the MetS is well known. Longitudinal studies have shown that hypogonadal patients are at an increased risk of the MetS.[80,81] However, studies have also shown that a patient with the MetS may develop hypogonadism eventually. Hypogonadism is often described as one of the components of the MetS. Therefore, hypogonadism and low testosterone probably has a role in the development of the MetS.

Physical inactivity and metabolic syndrome in COPD

COPD patients are generally physically inactive. Patients with stage – II and higher GOLD stage COPD have significantly reduced physical activity. There are variable reports regarding the association between physical inactivity and systemic inflammation. In a study by Watz *et al.* in subjects of COPD the MetS was associated with elevated levels of inflammatory markers and physical inactivity.[23] Physical inactivity in COPD can lead to increased weight gain and obesity thus predisposing the patients to develop MetS.[82]

Effect of steroid and risk of metabolic syndrome in COPD

Inhaled and oral steroids are used frequently but inappropriately to treat patients with COPD. Steroids affect most of the parameters of the metabolic syndrome.[83] The traditional clinical features of steroid overuse are diabetes, hypertension, dyslipidemia, and weight gain, usually presenting as central obesity with redistribution of body fat to truncal areas and dorsocervical and supraclavicular fat pads and the classic moon face.[84,85]

Impact of metabolic syndrome in COPD

COPD is complex disease with multiple systemic comorbidities and complications.[13] The comorbidities such as diabetes, hypertension, coronary disease, heart failure, and osteoporosis are more frequent when both COPD and MetS coexists.[86] COPD patients with the MetS have a more severe form of disease, more dyspnea, a lower FEV1 and require more inhalational glucocorticoids to control the disease.[22] The prevalence of MetS and its comorbidities increases with advancing age.[87] However, a recent study by Minas *et al.* has shown that MetS is also quite common among younger age group and in even subjects with a less severe form of COPD. COPD patients with MetS have higher leptin levels, low adiponectin and greater insulin resistance.[88] Thus this group of COPD subjects can be further stratified into a higher risk phenotype which requires a closer follow-up.

Conclusions and Future Perspectives

Metabolic syndrome is present in a large proportion of patients with COPD especially in younger patients and in those with a less severe form of COPD (GOLD stage I-II). Therefore, it may indicate that the risk of diabetes and its evolution and death related to premature cardiovascular diseases is likely to occur largely in a predominantly younger subset of COPD patients. Studies have shown that the presence of common underlying factors affects the natural history of both the diseases leading to significant morbidity and mortality. Thus, it is essential to focus on a comprehensive way of management of COPD and its comorbidities rather than primarily treating the pulmonary symptoms. So it is necessary to develop newer pharmacological agents which may modify the pathogenesis, thereby reducing the pulmonary and systemic complications of COPD. Studies have shown that COPD patients with MetS have more dyspnea and a greater risk of hospitalization either due to acute exacerbations, or other complications. Furthermore, certain studies have categorized this group into a definite COPD phenotype which requires special attention. Thus, it may warrant extensive research to elucidate the exact mechanisms to understand the relationship between MetS and COPD.

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Cite this article as: Naik D, Joshi A, Paul TV, Thomas N. Chronic obstructive pulmonary disease and the metabolic syndrome: Consequences of a dual threat. Indian J Endocr Metab 2014;18:608-16.
Source of Support: Nil, **Conflict of Interest:** None declared.