The metabolic syndrome, diabetes and lung dysfunction

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Abstract
Sleep-disordered breathing and sleep apnoea are conditions frequently associated with comorbidity, including obesity, diabetes, hypertension, insulin resistance (metabolic syndrome) and cardiovascular disease. The diabetic state (type 1 and type 2 diabetes) may be associated to diminished lung function and, in particular, decreased vital capacity, and the association between chronic obstructive pulmonary disease (COPD) and type 2 diabetes may be due to a shared inflammatory process. Also, the alteration in circulating endothelial progenitor cells found in respiratory disease, the metabolic syndrome and cardiovascular disease reflect a common condition of endothelial dysfunction.

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Résumé
Syndrome métabolique, diabète et dysfonction pulmonaire.
Des troubles respiratoires et des apnées du sommeil font partie d’un ensemble syndromique qui comprend obésité, diabète, hypertension, insulinorésistance (syndrome métabolique) et maladies cardiovasculaires. Le diabète, qu’il soit de type 1 ou de type 2, peut être associé à des altérations des fonctions respiratoires et notamment à une réduction de la capacité vitale. L’association entre bronchopneumopathie chronique obstructive (BPCO) et diabète pourrait être expliquée par un procès inflammatoire commun. L’altération des cellules endothéliales progénitrices mise en évidence au cours des affections respiratoires, du syndrome métabolique et des maladies cardiovasculaires pourrait avoir comme commun dénominateur une dysfonction endothéliale.

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1. Abbreviations

OSA obstructive sleep apnoea
CRP C-reactive protein
IL-6 interleukin-6
TNF-α tumor necrosis factor-alpha
CPAP continuous positive airway pressure
AHI apnoea/hypopnoea index
ICAM-1 intracellular adhesion molecule-1
FVC forced vital capacity
FEV forced expiratory flow
ARIC atherosclerosis risk in communities

NF-kB nuclear factor-kB
IGT impaired glucose tolerance
COPD chronic obstructive pulmonary disease
SDB sleep-disordered breathing
ER endoplasmic reticulum
EPC endothelial progenitor cells
MetSyn metabolic syndrome
PAH pulmonary arterial hypertension
VEGF vascular endothelial growth factor

2. Introduction

According to the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III), the metabolic syndrome is characterized by the following components, all of which are based on and related to insulin
resistance: impaired glucose tolerance; abdominal obesity; high triglyceride levels; decreased HDL cholesterol; and hypertension [1]. Insulin resistance is also accompanied by several other alterations not included in the diagnostic criteria for the MetSyn. An increase in prothrombotic factors, proinflammatory cytokines and endothelium dysfunction markers as well as the presence of microalbuminuria, non-alcoholic fatty-liver disease and/or non-alcoholic steatohepatitis, OSA and polycystic ovarian disease are all associated with insulin resistance [2].

MetSyn appears to be a systemic disease involving several organs and processes accompanied by a cluster of comorbidities. One of its most challenging aspects concerns the cellular mechanisms that link this constellation of metabolic abnormalities to the pathophysiological effects that later become manifest as the clinical disease.

It has been hypothesized that MetSyn, obesity and atherosclerosis have an inflammatory aetiology [3,4] and, in fact, the association of MetSyn with inflammation is well documented [5]. The increase in proinflammatory cytokines, including IL-6, resistin, TNF-α and CRP reflect overproduction by the enlarged adipose tissue mass. Evidence suggests that monocyte-derived macrophages reside in adipose tissue and might, at least in part, be responsible for generating proinflammatory cytokines locally and in the systemic circulation [6,7].

There is increasing evidence that insulin resistance in the liver, muscles and adipose tissue is not only associated with an abundance of proinflammatory cytokines (and the relative deficiency of the anti-inflammatory cytokine adiponectin), but is its direct result. In addition to adipose tissue, an inflamed liver can be an important source of systemic factors leading to the development of insulin resistance [8]. The proinflammatory states of obesity and MetSyn, probably a result of overnutrition [4], induce insulin resistance, leading to clinical and biochemical manifestations of MetSyn.

SDB and COPD are characterized by an inflammatory state and the release of proinflammatory cytokines such as IL-6 and TNF-α [9]. This inflammatory mechanism may, in turn, explain the insulin resistance and glucose intolerance observed in these patients and, in particular, the association between MetSyn and lung dysfunction. It has also been hypothesized that the hypoxaemia seen in SDB and in lung dysfunction is a predictor of the degree of metabolic disorder.

3. The metabolic syndrome and sleep apnoea

OSA is a prevalent disorder particularly among middle-aged, obese men, although its presence in women as well as in lean individuals is being increasingly recognized. Indeed, 17–24% of adult men and 5–9% of women demonstrate an AHI of more than five events per hour, the originally proposed criteria for sleep apnoea [10]. A large majority of adult sleep apnoea sufferers present with many of the features of MetSyn. There is, in fact, a strong association between OSA and obesity, particularly the central android-type of obesity, and hypertension and glucose intolerance. Abdominal and neck adiposity predisposes to OSA and restrictive lung disease in patients with MetSyn.

On the other hand, OSA has recently been recognized as a risk factor for cardiovascular disorders and MetSyn [11,12]. Just as two-thirds of OSA patients are obese, two-thirds of obese persons have OSA, with a cardiovascular odds ratio of 4 [10]. According to Vogt et al. [13,14], there is a stronger correlation (assessed by computed tomography scanning) between visceral rather than subcutaneous or total fat and indices of sleep apnoea. Visceral intra-abdominal fat accumulation appears to be a more important risk factor for OSA in obese subjects than subcutaneous fat in the neck or parapharyngeal regions [15]. On the other hand, insulin resistance has been implicated in the pathogenesis of MetSyn and is primarily correlated to the amount of intra-abdominal visceral fat.

Several clinic-based studies have hypothesized that SDB is associated with insulin resistance and glucose intolerance. The Sleep Heart Health Study reported that it is independently associated with insulin resistance and glucose intolerance [16]. It is also associated with higher odds of metabolic disorders after adjustment for several confounding covariates, including age, gender, smoking status, body mass index and waist circumference. The severity of SDB, as assessed by the respiratory disturbance index and the degree of hypoxaemia, was also found to be independently associated with the degree of insulin resistance. In a study by Ip et al. [17], involving 185 patients with OSA and an AHI greater than 5, it was found that insulin resistance increased with age and the degree of obesity, although multiple linear-regression analysis revealed that obesity was the main determinant of insulin resistance. Moreover, parameters of SDB were found to be independent determinants of insulin insensitivity, a finding that was confirmed by other authors using different approaches [18,19]. Tassone et al. [19] showed that obese individuals with OSA are more insulin-resistant than patients who are only obese as they are specifically impaired in terms of hepatic insulin sensitivity. The association between OSA and insulin resistance has even been found in non-obese subjects as well as in those with mild forms of sleep apnoea [16]. The two-way association between OSA and insulin resistance is supported by the fact that sleep apnoea is a frequent symptom in those with polycystic ovary syndrome (PCOS) in which insulin resistance is a primary pathophysiological abnormality [20].

Sleep apnoea and sleep deprivation not only lead to insulin resistance but, as a consequence, to impaired glucose tolerance as well [21]. Several studies have shown an increased prevalence of sleep apnoea and SDB in patients with type 2 diabetes [22,23]. The Wisconsin Sleep Cohort Study demonstrated that self-reported diabetes was three to four times more prevalent in subjects with a high AHI score [24]. The Nurses’ Health Study cohort [25] and a Swedish study [26] showed that both diabetes and hypertension are strongly associated with OSA. According to these prospective studies, SDB significantly increases the risk of type 2 diabetes in the general population over a 10-year period.

As for the pathophysiological dysfunction seen in OSA, hypoxaemic stress apparently plays a crucial role in the development of metabolic disorders. The hypoxia seen in animal studies and in humans during exposure to high altitudes is associated with a significant decrease in insulin sensitivity [27,28]. Hypoxia
could lead to insulin resistance and glucose intolerance by promoting the release of proinflammatory cytokines, such as IL-6, IL-8, ICAM-1 and TNF-α, which are higher in patients with OSA than in control subjects [13]. An elevation in CRP has also been reported in patients with OSA [29]. In obese mice, hypoperfusion and hypoxia in adipose tissue underlie the dysregulated adipocytokine production [30], which is mediated by ER stress and post-transcriptional regulation. Local adipose tissue appears to be partly responsible for dysregulated adipocytokine production and MetSyn in obesity. Hyperleptinaemia has also been observed in patients with OSA and may be related to the higher amounts of visceral fat and cytokines [13]. Other atherogenic risk factors associated with OSA and MetSyn are the increases in fibrinogen, plasminogen activator inhibitor (PAI), D-dimer and microalbuminuria.

There are other pathways by which SDB can lead to metabolic dysfunction. Numerous studies have shown that these patients exhibit hyperactivity of the hypothalamic–pituitary–adrenal axis. According to Spiegel et al. [21], SDB, sleep fragmentation and intermittent hypoxia induce an increased sympathetic output, elevated evening cortisol levels and an enhanced ACTH response to corticotropin-releasing hormone (CRH). In addition, impaired gonadal and GH/IGF-1 axis activity has been described in patients with OSA or sleep fragmentation [31]. SDB probably reinforces the endocrine pattern that characterizes and favours the development of the glucose, lipid and haemodynamic disorders seen in MetSyn.

All of the pathogenetic mechanisms of the inflammatory, metabolic and endocrine disorders associated with SDB could be caused by the hypoxaemic state. Hypoxia per se as well as the signals mediated by hypoxia could be therapeutic targets for the treatment of MetSyn associated to OSA. However, although CPAP treatment should presumably improve the insulin resistance and the metabolic disorders, conflicting results have been reported [32]. While studies by Brooks et al. [22] and Harsch et al. [18] demonstrated an improvement in insulin sensitivity associated with a significant decrease in subclinical inflammatory parameters after three to four months of CPAP, other investigators have been unable to confirm these findings.

4. Lung dysfunction and diabetes

Diabetes may be either a cause or a consequence of SDB, or it may be both. The diabetic status is associated with periodic breathing, a respiratory disorder induced by abnormal central respiratory control [33]. Among the participants of the Sleep Heart Health Study [32], the prevalence of periodic breathing was 5.4% and 2.5% in diabetics and in non-diabetics, respectively, with an odds ratio of 2.23. However, as type 2 diabetes is also associated with obesity, this may have an effect on the relationship.

Ventilation restriction has frequently been described in diabetic patients in recent decades. A pattern of modest lung restriction and reduced diffusion capacity [34] has been found in type 2 diabetic patients without overt cardiopulmonary disease, but with proportional decreases in FVC and forced expiratory flow (FEV1) function [35–38].

The Third National Health and Nutrition Examination Survey (NHANES III) [39] found that previously diagnosed diabetics have an FEV1 lower than that of non-diabetics. Impaired lung function was also greater in patients with poorly controlled diabetes, a finding that is not explained by either obesity or increasing age. A similar association was also seen between glycaemic markers and FVC. The Framingham Offspring Cohort and the Heart and Health Study demonstrated an association between diagnosed diabetes and plasma hyperglycaemia with reduced FEV1 [38–40]. The longitudinal population analysis in the Copenhagen City Heart Study [37] revealed an association between newly diagnosed diabetes and impaired pulmonary function with an annual 25 mL greater decrease in FEV1 in diabetics compared with controls. In a recent cross-sectional analysis in the ARIC Study [41], Yeh et al. showed that type 2 diabetics have significantly lower FVC and FEV1 compared with non-diabetics. These alterations correlated with the degree of hyperglycaemia, duration of diabetes and intensity of antidiabetic treatment. In a prospective analysis, the FVC was found to decline faster in diabetics than in non-diabetics and showed graded associations with indicators of diabetes. These results suggest that alterations in lung function precede diabetes and continue after its onset, and that the physiological annual FVC decline tends to accelerate with diabetes duration [40]. Also, the adverse effects of diabetes and glycaemic values on pulmonary function were stronger among smokers, suggesting that there is an interaction between hyperglycaemia and tobacco-smoking.

Hyperglycaemia is also associated with poor outcomes in pneumonia and in acute exacerbations of COPD as well as in myocardial infarction and stroke. In addition, hyperglycaemia at the time of admission predicted failure of non-invasive ventilation and infectious pulmonary complications in patients admitted to intensive care with acute respiratory failure due to COPD [42]. In a retrospective study, Baker et al. [43] demonstrated that, in patients with COPD, the absolute risk of an adverse outcome (death or a hospital stay longer than nine days) was significantly increased if random blood glucose was greater than 7 mmol/L.

In patients with type 1 diabetes, abnormal lung function is detected in up to 73% of young asymptomatic patients [44] with reductions of 8–20% in both FVC and FEV1, which is consistent with a modest restrictive defect [37,45]. Total lung capacity and end-expiratory lung volume are reduced by about 30%, and are inversely related to glycated haemoglobin levels in longstanding type 1 diabetes [45]. The mechanical impairment may be related to collagen glycation of lung parenchyma and alveolar microangiopathy. In fact, a significant reduction in lung diffusion capacity has been reported in type 1 diabetics, especially in poorly controlled patients [46]. The deficit in lung diffusion capacity is also correlated to the prevalence of retinopathy, nephropathy and neuropathy [46].

Pulmonary structural disorders are the same of those found in the retina, kidney and skeletal muscle of type 1 diabetics [47]. In both human and animal studies, diabetic lungs have demonstrated diabetic microangiopathy of the alveolar septal capillaries, with a thickened epithelial and capillary basement.
membrane, and increased extracellular matrix and connective tissue [48,49].

The mechanisms by which impaired glycaemic control may lead to a reduction in lung function may also be supported by systemic inflammation [37]. Alternatively, by inducing increased oxidative activity, intracellular NF-kB and inflammatory mediator expression, chronic hyperglycaemia can also bring about a rise in collagen molecule synthesis and cross-linking via the acceleration of advanced glycation end-products, which can also negatively influence lung function.

On the other hand, SDB or a pulmonary disease could favour the onset of either IGT or diabetes. According to a 12-year follow-up study in a middle-aged Malmo population [50], sleep difficulties and short sleep duration are associated with an increased risk of diabetes. Disturbance and curtailment of sleep have also been shown to have an impact on metabolic parameters. Experimental sleep deprivation has been found to result in disturbances in glucose metabolism and in sympathetic–vagal imbalance. Impaired lung function has attracted growing interest as a potentially novel risk factor for glucose intolerance and type 2 diabetes. The ARIC Study [51] showed that lower vital capacity is an independent predictor of incident type 2 diabetes.

COPD is often associated with diabetes or IGT [52,53], and nearly half of all COPD patients have one or more components of MetSyn [52,54]. Diabetes is independently associated with reduced lung function that, together with obesity, could further worsen its severity [57]. According to the ARIC Study and the Nurses’ Health Study [52,55], patients with COPD have a 1.8–2.0 relative risk of developing type 2 diabetes. The former, a prospective cohort study involving almost 100,000 women with COPD, showed a statistically significant higher risk of developing type 2 diabetes that persisted after multivariate adjustment for potential confounders. Increasing evidence now indicates that proinflammatory cytokines such as CRP, IL-6 and TNF-α may play a role in the pathogenesis of type 2 diabetes. In the ARIC Study, the circulating white cell count, fibrinogen and lower serum albumin predicted the development of type 2 diabetes [52]. Sonnenberg et al. [56] hypothesized that TNF-α might be a mediator in the diabetic process. This particular cytokine activates the NF-kB, upregulates adhesion molecules and increases oxidative stress. Together with TNF-α, oxidative stress may provide a stimulation pathway that interferes with glucose metabolism, although no such association was found in women with asthma. Differences in the inflammation and cytokine profiles between COPD and asthma patients might explain why the former, but not the latter, have an increased risk of type 2 diabetes.

Improvement in lung function following CPAP resulted in significant improvements in inflammatory parameters, glucose control and glycated haemoglobin [57] in diabetic patients.

### 5. Circulating progenitor cell alterations in metabolic and pulmonary diseases

One of the most exciting and recent advances in the knowledge of chronic disease pathogenesis is the recognition that bone marrow–derived progenitor cells have the ability to repopulate different tissues in addition to the haematopoietic lineages. Once these cells have reached the bloodstream, they are involved in repair and regeneration of the myocardium, endothelium, smooth and skeletal muscles, epithelium, bone and cartilage. Disturbance in one or more of these progenitor cell lineages may result in an inability to maintain homoeostasis in the target tissue, thus favouring disease development in predisposed subjects and/or in the presence of damaging triggers. We discuss here the hypothesis that alterations of circulating progenitor cells constitute a potential link between metabolic and respiratory diseases.

Many clinical conditions and risk factors have been associated with alterations in generic or committed progenitor cells in bone marrow and in the circulation, and such findings have been hailed as a novel mechanism that mediates disease development and progression [58]. Specifically, the classical risk factors for atherosclerosis are associated with a reduction of circulating EPC, and this is currently considered one mechanism by which risk factors impair function of the vascular endothelium. In experimental models, EPC play a role in virtually all events that lead to vascular damage. In humans, the amount of circulating EPC is related to non-invasive measures of endothelial function, and predicts the extent and progression of atherosclerosis as well as the occurrence of cardiovascular events [59]. Moreover, lifestyle and pharmacological interventions aimed at lowering cardiovascular risk can also consistently modulate EPC. Indeed, there are plenty of data to suggest that EPC reflect the global health of the cardiovascular system.

Accumulating evidence also suggests that all of the clinical features of MetSyn are strongly associated with EPC alterations. Individual studies indicate that dysglycaemia, hypertension, obesity and dyslipidaemia lead to EPC depletion and/or dysfunction [60,61]. To explore the effect of clusters of these risk factors on progenitor cell levels, we studied a population sample with a wide range of metabolic disturbances and found that circulating progenitor cells are synergistically reduced by clustered MetSyn components [62]. Thus, we hypothesize that a defect in the stem-cell compartment is one mechanism that could account for the high incidence of vascular damage in patients with MetSyn.

However, endothelial damage is not pathognomonic of cardiovascular and metabolic diseases but, instead, represents a common pathophysiological response in many medical conditions—both acute and chronic [63]. Interestingly, recent advances have defined a role for endothelial dysfunction in the pathogenesis and progression of parenchymal and vascular lung diseases. For instance, an alteration in endothelial integrity is considered the primum movens in the development of fibroproliferative lesions in primary pulmonary hypertension [64]. Similarly, chronic hypoxia in patients with lung pathology is thought to contribute to the endothelial cell apoptosis that favours the appearance of secondary pulmonary hypertension [65]. Indeed, the endothelium is also gaining increasing interest in novel theories of COPD, especially emphysema. Finally, indirect evidence of endothelial dysfunction has been found in patients with OSA, who often have underlying MetSyn.

For these reasons, we here suggest that endothelial dysfunction could represent the common ground between both
metabolic and pulmonary diseases. Given the major contribution of circulating EPC to endothelial regulation, we speculate that impairment of the EPC compartment might be the key to understanding the association between these diseases, despite their apparent differences.

We addressed this issue by, for the first time, measuring circulating EPC in patients who have severe hypoxic lung disease [66]. We found that EPC were markedly reduced in hypoxemic patients compared with controls, and this reduction was directly related to disease severity in both obstructive and restrictive lung disease. Our data indicated that the depletion of circulating EPC in these patients was due to increased apoptosis, possibly related to hypoxia, and to a type of bone marrow exhaustion, possibly related to the chronic nature of the disease. These results have been reproduced by another group of researchers, who showed a reduction of circulating EPC in the presence of COPD, and an inability of these patients to upregulate EPC after exercise [67]. As exercise is known to be a potent stimulus for EPC mobilization from the bone marrow in healthy subjects, these data strengthen the hypothesis that progenitor cell decline is related to bone marrow unresponsiveness or exhaustion. Moreover, an inverse relationship was observed between levels of EPC and TNF-α, a cytokine that mediates inflammatory processes in both COPD and MetSyn [68], suggesting that chronic sterile inflammation contributes to the association between these two conditions.

In patients with MetSyn, abdominal and neck adiposity predisposes to OSA and restrictive lung disease. The link between MetSyn and OSA is primarily mechanical, but the biological pathways subsequently leading to vascular and parenchymal lung remodeling, as well as to the increase in pulmonary pressure and cardiovascular risk, include inflammation and endothelial damage.

The role of EPC in the pulmonary circulation is supported by a variety of experimental studies. In a rat model of monocrotaline-induced pulmonary hypertension, EPC administration was able to prevent or even reverse vascular lesions, and to decrease pulmonary pressure [69]. These and other data appear to be so strong that there are already two ongoing trials of cell therapy using EPC in patients with PAH [70]. Remarkably, de la Peña et al. found that, in patients with OSA free of cardiovascular risk factors, there was a lower level of circulating EPC that inversely correlated to an increased concentration of VEGF, a typical remodeling cytokine in the pulmonary circulation [71]. Thus, EPC impairment appears to underlie both MetSyn and OSA, thus revealing a potential pathogenic link.

On this basis, we hypothesize that EPC reduction in MetSyn patients is not only related to an increased risk of cardiovascular events, but also to adverse lung remodeling favouring OSA, hypoxic syndromes and pulmonary hypertension. Indeed, cardiovascular and respiratory diseases both display striking similarities in terms of EPC regulation [72]. In both conditions, predisposing risk factors (such as diabetes and smoking) reduce EPC, which are then further depleted in the presence of chronic disease according to its severity (for example, atherosclerotic burden and degree of hypoxia). Finally, when acute events occur (such as myocardial infarction or respiratory distress), EPC are transiently upregulated in both conditions, and the preserved ability to mobilize EPC from bone marrow is an independent predictor of a more favourable outcome [73]. Thus, EPC dysregulation, as extensively seen in patients with MetSyn or its components, may predispose to both atherosclerotic cardiovascular and pulmonary disease, and to adverse outcomes after acute events.

Nevertheless, we would also like to provokingly suggest a possible reverse interpretation of this pathophysiological connection, such that low levels of EPC, as seen in patients with cardiovascular and respiratory disease, may predispose to the development of insulin resistance and MetSyn. While this model seems to be counterintuitive, there are data to suggest that endothelial dysfunction—which is common to both these conditions—may be the cause as well as the consequence of insulin resistance. Indeed, the metabolic effect of insulin—that is, the uptake of glucose by peripheral tissues—requires normal microcirculation regulation and perfusion. When this physiological vascular–metabolic coupling is interrupted, as in the case of systemic endothelial dysfunction, insulin action is impaired and insulin resistance may ensue. In this light, a reduction of EPC, associated with lung disease through the impairment of microcirculatory endothelial function, may represent another mechanism of predisposition to MetSyn and diabetes.

We have reviewed here some intriguing data to suggest that changes in circulating EPC can lead to endothelial dysfunction which, in turn, can increase the risk of cardiovascular, respiratory and metabolic abnormalities. Although more data are needed to support this hypothesis, the resulting picture reveals a fascinating connection between disparate phenotypes that can be traced back to the central compartment from which stem cells originate: the bone marrow.

6. Conclusion

SDB is a prevalent condition associated with significant comorbidity such as obesity, diabetes, hypertension, insulin resistance and cardiovascular disease. It has been seen that the severity of insulin resistance is correlated to the degree of SDB. Data from the literature support a two-way, pernicious association between sleep apnoea and insulin resistance. Visceral obesity and its consequential insulin resistance may, indeed, be the principal culprit leading to sleep apnoea which, in turn, can accelerate these metabolic abnormalities, possibly through the progressive elevation of stress hormones and cytokines (Fig. 1). Sleep apnoea can be considered an important clinical aspect of the metabolic syndrome as well as of hepatosteatosis or cardiovascular complications. A new version of syndrome X or the metabolic syndrome has recently been proposed. Called “syndrome Z”, it describes the interaction of sleep apnoea and the metabolic syndrome.

The diabetic state is associated with diminished lung function and, in particular, a decreased vital capacity that precedes its onset, and is then affected by its duration and severity. In type 1 diabetes, the systemic microangiopathy appears to involve the alveolar diffusion capacity of the lungs, as with other target organs. The association between COPD and type 2 diabetes

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may be explained by a common inflammatory process [74]. The shared mechanism by which major risk factors such as diabetes, obesity, hyperlipidaemia and hypertension can lead to chronic disease is systemic inflammation. According to Fabbri and Rabe [75], diagnosis of a “chronic systemic inflammatory syndrome” can be established if at least three out of six components are present: age older than 40 years; smoking more than 10 packs a year; symptoms of abnormal lung function compatible with COPD; chronic heart failure; the metabolic syndrome; and increased CRP. These authors also emphasized the importance of complex risk factors in the development not only of the primary disease (COPD or MetSyn), but also of systemic and complex abnormalities affecting other organs.

Changes in the circulating endothelial progenitor cells found in respiratory diseases, the metabolic syndrome and cardiovascular disease reflect a common state of endothelial dysfunction, and further support a link between the respiratory, cardiovascular and metabolic abnormalities.

As part of the natural history of diabetes, the lungs may be yet another target of diabetic injury. Primary care physicians and diabetologists should, therefore, monitor pulmonary function in their diabetic patients.

References


