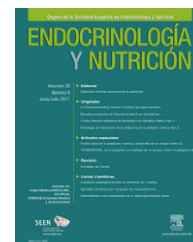




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## EDITORIAL

### Type 2 diabetes and the lung: A bidirectional relationship<sup>☆</sup>

### Diabetes mellitus tipo 2 y pulmón: una relación bidireccional

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Because of its great vascularization and abundant collagen and elastin fibers, the lung parenchyma is a target organ sensitive to the harmful effects associated with diabetes mellitus. Histological changes such as mucosal secretion changes, thickening of the basal membrane of the lung epithelium, decreased alveolar space, a higher degree of fibrosis, centrilobular emphysema, and pulmonary microangiopathy have been reported in patients with diabetes.<sup>1</sup> Multiple observational studies have shown impaired lung function, usually as modest restrictive changes.<sup>2</sup> Such changes, attributed to a greater rigidity of the lung parenchyma and the chest wall or to the microvascular damage induced by diabetes, have to date been of little clinical relevance, although it should be borne in mind that, in diabetic patients, a 10% reduction in forced expiratory volume in the first second (FEV1) has been associated with an increased overall mortality.<sup>3</sup> This secondary clinical role is largely due to the nonexistent therapeutic implications derived from this knowledge to date, in contradistinction to the impact of other target organs of diabetes such as the kidney, retina, peripheral nervous system, or cardiovascular system. However, the relationship between endocrinologists and pneumologists is being redefined as a result of improved understanding of the harmful effects of diabetes not only on lung parenchyma, but also on the mechanisms involved

in the control of ventilation and the maintenance of upper airway patency.

In parallel to the increase in the prevalence of obesity and type 2 diabetes mellitus in recent decades, there has been a great increase in the number of patients referred to sleep units for studies of the obstructive sleep apnea syndrome (OSAS), for which obesity is the main determinant factor. OSAS is characterized by the occurrence of repeated episodes of upper airway obstruction (apnea) during sleep leading to sleep fragmentation, as well as changes in intrathoracic pressure and intermittent hypoxia. Evidence from clinical series<sup>4</sup> and population studies<sup>5</sup> relating OSAS to an increased cardiovascular morbidity and mortality has gradually accumulated.

Intermittent hypoxia, a feature which is virtually exclusive to sleep respiratory disorders, plays a central role in the increase cardiovascular risk of OSAS. It is known to exert its effects partly through its metabolic consequences, promoting dyslipidemia<sup>6</sup> and altering glucose metabolism. Intermittent hypoxia increases insulin resistance and decreases insulin secretion. Various pathophysiological mechanisms have been implicated in these effects, including sympathetic activation, activation of lipid synthesis at the liver, induction of inflammation, changes in adipokine synthesis, and activation of the hypothalamus–adrenal axis.<sup>7</sup> As a result, OSAS is associated with insulin resistance in non-diabetic subjects,<sup>8</sup> and also acts as a risk factor for the occurrence of type 2 diabetes mellitus in the general population.<sup>9,10</sup> The clinical relevance of these findings is supported by observations which suggest an improved control of diabetes when OSAS is treated.<sup>11,12</sup>

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Alternatively, there are observations which suggest a marked impact of the presence of insulin resistance and diabetes on respiratory changes in obese subjects. The Sleep Heart Health Study, a population study, showed a greater severity of OSAS and nocturnal hypoxia in subjects with type 2 diabetes mellitus,<sup>13</sup> supporting some prior clinical observations.<sup>14</sup> Although this effect disappeared when the analysis was adjusted for the presence of obesity and other confounding factors, subsequent studies have provided new findings in this regard. In women with morbid obesity, a phenotype with a high prevalence of frequently asymptomatic OSAS,<sup>15</sup> who were carefully matched in accordance with the main variables involved in its occurrence, the presence of type 2 diabetes was an independent risk factor for the development of severe hypoxemia during sleep.<sup>16</sup> Several pathophysiological mechanisms may have been involved in these findings. Lung function impairment in these types of patients is mainly characterized by a decreased FEV1 related to the presence of both diabetes<sup>17</sup> and insulin resistance.<sup>18</sup> However, it could not be related to nocturnal hypoxia.<sup>16</sup> The reported presence of glucagon-like peptide-1 (GLP-1) receptors in human lung and the fact that experimental administration of GLP-1 to human pneumocytes increases the production of lung surfactant, which is partly responsible for maintaining airway patency suggest another potential pathophysiological mechanism relating type 2 diabetes mellitus to lung function impairment.<sup>19,20</sup> Diabetes may also alter central respiratory control mechanisms, as is suggested by the increased number of periodic breathing episodes during sleep associated with it.<sup>13</sup> Diabetic autonomic neuropathy may cause changes in reflex mechanisms responsible for maintaining the patency of the upper airway or may condition, through an increased circulation time due to the presence of autonomic heart disease, a defective response of the peripheral and central chemoreceptors to episodes of intermittent hypoxia. All these factors would result in greater ventilatory instability and would explain the increased number of episodes of obstructive and central apnea in diabetic patients with autonomic neuropathy as compared to those with no neuropathy.<sup>21,22</sup> The increase in proinflammatory cytokines such as tumor necrosis factor (TNF)  $\alpha$  induced by obesity or insulin resistance has also been related to impaired lung function<sup>23</sup> or the occurrence of sleep apnea.<sup>24</sup>

Not only has the possibility of improved diabetes control when sleep respiratory disorders are treated aroused interest, but the apparent bi-directionality of the relationship has also opened up complementary alternatives of potential clinical relevance. Data from animal experiments have suggested that increases in insulin sensitivity induced by the administration of metformin have beneficial effects on nocturnal apnea episodes.<sup>25</sup> No studies assessing the impact of improved glycemic control on respiratory parameters during sleep in humans are currently available, so we believe that further research is needed on this subject.

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