

## Diabetic Lung: A Sweet Kiss of Impending Death

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Lung is one of the least studied organs in diabetes. Global data in support of toxic impact of hyperglycemia on lung health threaten the researcher about surge in mortality as well as associated morbidity. A recent report released by the World Health Organization reveals that there were 1.5 million (2.7%) deaths caused by diabetes in 2012, up from 1.0 million (2.0%) in 2000, while major cause of death in diabetic patients is glucotoxicity-induced complications. Apart from this in 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) and the United States (17.7 million) in second and third place respectively. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India [1,2].

Increasing evidence reveal that lung is also one of the target organs for diabetic microangiopathy in patients with either type 1 or type 2 DM. It is a known fact that the lung microvascular system has huge reserve function, hence diabetic lung damage is quite subclinical and often ignored by patients and physicians, however with continued increase in the occurrence of diabetes in relatively young population, more and more pulmonary dysfunction is likely to be attributed to diabetic pulmonary complications [3]. It was also endorsed that, diabetes includes a predisposition to infections and chronic obstructive pulmonary disease such as pneumonia, asthma, pulmonary fibrosis, and pulmonary tuberculosis as well as impaired breathing during sleeps [4,5]. In a recent meta-analysis including 34 studies from 24 manuscripts (10 case-control studies and 24 cohort studies) highlighted that Diabetes was significantly associated with the increased risk of lung cancer compared with non-diabetic controls though few researcher condemn it [6]. Besides this increased incidence of the idiopathic respiratory distress syndrome (IRDS) in infants of diabetic mothers may be explained by metabolic derangement and responsible for the inadequate production of surfactant. Experimental studies of the underlying mechanisms in the lungs of fetuses of pregnant diabetic rats have shown a decreased formation of the two major surfactant phospholipids desaturated phosphatidyl choline and phosphatidyl glycerol. In addition, the activities of key enzymes responsible for the production of these phospholipids are decreased in the fetal lung tissue. In addition to this inadequate utilization of pulmonary glycogen for surfactant biosynthesis has also been observed [7].

Chronic metabolic abnormalities due to insulin deficiency or resistance, along with hyperglycemia, cause systemic oxidative stress and inflammation which impair antioxidant defense, leading to cardiovascular dysfunction as well as development of fibrosis in multiple organs, including the heart, kidneys, and lungs. Glycation of hemoglobin affecting oxygenation, decrements in the lung function of patients with diabetes are believed to be the consequence of biochemical alterations in the connective tissue constituents of the lung, particularly collagen and elastin, as well as microangiopathy due to the non-enzymatic glycosylation of proteins induced by chronic hyperglycemia [8,9]. Besides this systemic impact of diabetes with excessive NO combined with ROS, may directly contribute to platelet activation and cause chronic inflammation associated with damaged lung capillary endothelium and microangiopathy. NO is enzymatically synthesized from L-arginine and molecular oxygen by NO synthase (NOS) and plays a critical role in the regulation of pulmonary circulation during physiological as well as patho physiological circumstances. Excessive NO may out-compete antioxidants for ROS, scavenging, forming secondary RNS products, such as nitrosonium cation (NO<sup>+</sup>), nitroxyl anion (NO<sup>-</sup>), and peroxy nitrite (ONOO<sup>-</sup>). These RNS products may also play a role in the development of fibrosis and modulate platelet function causing additional oxidative stress, microvascular dysfunction and injury. Platelets play a significant role in acute lung injury in initiating inflammation, increasing microvascular leakage, and promoting ventilation/perfusion mismatch. They contribute to redox imbalance through production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), pro-leak molecules, and recruitment of inflammatory cytokines and leukocytes to the damaged endothelium. Therefore in the presence of excess super oxide in the diabetic lung, bioavailable NO may be depleted, affecting vascular tone and endothelial function, while production of toxic reactive nitrogen species causes vasoconstriction and enhanced endothelial injury. However, decreased pulmonary capillary blood flow was associated with the duration of diabetes according to some physiological research [10,11].

Alterations in collagen and elastin along with microangiopathy result in thickening of the alveolar epithelial basal lamina, leading to reduced pulmonary capacity for the diffusion of carbon monoxide, which is a measure of gas conductance across alveolar tissue membrane into capillary erythrocytes and subsequent chemical binding to hemoglobin. Cross-sectional analyses shown that adults with diabetes have 3 - 10% lower lung volumes (FVC more consistently than FEV1) compared with adults without diabetes, independent of BMI and smoking status. Contrary to the cross-sectional studies, findings in longitudinal studies have been less consistent. Some have shown that adults with diabetes have an accelerated decline in lung function over time and the decline correlates with blood sugar control or duration of diabetes, supporting the hypothesis that the lung can be a target organ in diabetes. However, other longitudinal studies have not confirmed a greater decline in lung function over time in diabetic patients [12-16].

Recently it has been explored that, neuroadrenergic bronchopulmonary denervation may also occur in diabetic patients with autonomic neuropathy as well as neuroadrenergic denervation of the lung is associated with the decline of respiratory functional indexes leading to lung diastolic stress disorder. Moreover Non- adrenergic Non-cholinergic neurotransmitter release is decreased due to diabetic autonomic neuropathy, which could deregulate the pulmonary vascular tone and pulmonary ventilation [12].

Therefore available data clearly support an association between diabetes and lung function, however the definitive direction as well as the exact pathophysiological mechanism to explain this association is unclear. Moreover the role of diabetic autonomic neuropathy and its impact on lung mechanics has yet to be fully explored. Therefore, more studies should focus on the neuro physiology of the diabetic lung in the future for better understanding of the link between lung function and diabetes as well as directionality of this association, will offer invaluable insights into design of therapeutic approaches for diabetic lung to shield the society from sweet kiss of impending death.

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