Role of Diabetes in the Lung injury

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Abstract: Diabetes mellitus is a chronic, progressive metabolic disorder whose incidence is steadily increasing worldwide. Diabetes causes systemic damage to the body, leading to chronic inflammation and impaired immune function, and is easily complicated by serious infections. Over the past decade, an increasing number of studies have focused on lung injury in diabetes. Diabetes is a common disease in the ICU, and a better understanding of the relationship between the diseases is of great importance for clinical management. This reviews the advances in epidemiology, pathophysiology, and therapeutic management.

Keywords: Diabetes; Lung Injury; ARDS; Mechanism

1. Introduction

Diabetes mellitus (DM) and its associated complications are a global health problem[1]. According to the statistics of the International Diabetes Federation in 2019, the number of diabetic patients worldwide has exceeded 460 million, and this number is expected to increase in the future[2]. Previous studies have reported diabetes-related lung diseases, such as reduced lung function, pulmonary microangiopathy, and pulmonary hypertension.

Due to the close relationship between diabetes and lung injury, assessing the risk factors for the occurrence and prognosis of diabetes combined with lung injury will help to identify people at risk of organ dysfunction early and provide some guidance for early prevention and treatment.

2. Underlying mechanism

The pathophysiology of diabetic lung injury is complex, multifactorial, and not fully understood. Underlying mechanisms include hyperglycemia, hyperinsulinemia, autonomic neuropathy, inflammatory, oxidative stress, alveolar capillary and pulmonary arteriolar microangiopathy, impaired lung function, surfactant dysfunction, and respiratory muscle dysfunction.

2.1 Inflammation

Previous studies have shown that circulating levels of acute phase proteins (such as C-reactive protein (CRP), haptoglobin, fibrinogen, plasminogen activator inhibitor, and serum amyloid A) and sialic acid, as well as cytokines and chemokines, are elevated in patients with T2DM[3, 4]. The inflammatory storm plays an important role in the onset and development of ARDS. The inflammatory response is likely to contribute to the occurrence of T2DM by causing insulin resistance, which in turn is enhanced in the presence of hyperglycemia to promote long-term complications of diabetes[5]. The triggering mechanisms of inflammation in T2DM are still poorly understood. Possible mechanisms involved: hypoxia, cell death, NF-κB and JNK pathways, IL-6 and insulin resistance, IL-1 system as a sensor of metabolic stress, and adipokines[6].

2.2 Oxidative stress

Hyperglycemia is thought to contribute to the development of vascular dysfunction in diabetes through oxidative stress[7]. In chronic hyperglycemia and diabetes, NADPH oxidase is activated, leading to increased ROS in the lung and pulmonary vasculature[8]. John and colleagues[9] found that hyperglycemia increased pulmonary vascular permeability and vascular superoxide. Moreover, inhibition of NADPH oxidase or management in chronic glycemic control could improve pulmonary vascular permeability.

2.3 Immunosuppression

Several studies have shown that most diabetic patients have immunosuppression, such as abnormal adhesion, chemotaxis, and phagocytosis of neutrophils. In COVID-19 patients with diabetes, the levels of immune-related biomarkers (including C-reactive protein, serum ferritin, and IL-6) and the incidence of lymphopenia were higher[10]. The expression level of angiotensin-converting enzyme II on the surface of monocytes/macrophages, the level of secreted IL-1β, and the level of viral load in the cells are all positively correlated with the blood glucose concentration in the culture medium under different blood glucose concentrations[11]. Due to mild chronic inflammation in the development of diabetes, patients are more prone to cytokine storms leading to systemic organ failure.

2.4 Coagulation

A major pathophysiologic feature of ARDS is coagulopathy, manifested by tissue factor (TF) exposure, pathway activation, anticoagulant dysfunction, microvascular thrombosis, and endothelial injury. Lorente also found that in ARDS patients with diffuse alveolar damage (DAD), P/F ratio and dynamic respiratory compliance were lower, SOFA scores and INR were higher, and death from hypoxemia was more likely[12]. In addition, prolonged INR has been reported as an early prognostic indicator of severe ARDS in patients with COVID-19 [13].

2.5 Lung Function

Diabetic microangiopathy can involve alveolar tissue and capillaries, leading to restriction of lung volume and alveolar gas transport, as manifested by the reduced diffusing capacity of the lung for carbon monoxide (DLCO), as well as its components: membrane diffusing capacity and pulmonary capillary blood volume (VC)[14]. WILLIAM and colleagues found that a modest loss of alveolar-capillary reserves can be quantified by noninvasive methods independent of physical fitness and correlates with glycemia as well as systemic microangiopathy[15]. Others showed that diabetic polyneuropathy impairs respiratory neuromuscular function[16], potentially affecting pulmonary volumes.

3. Effect of diabetic management

Diabetes is a confounder and other factors associated with diabetes treatment or management are truly related to the variable risk of developing lung injury.

3.1 Insulin

The notion that the effects of insulin extend far beyond simple glycemic control is now well established. In animal and clinical studies of critical illness, insulin is immunomodulatory. Independent of glycemic control, insulin has been shown to modulate inflammation via the mannose-binding lectin pathway, nuclear factor-κB, and through an alternation of proinflammatory and anti-inflammatory cytokines[17, 18].

3.2 Oral drugs

Insulin is not the only diabetic treatment that may modulate the development of ALI. Agonists of PPAR-γ and

metformin have been shown to reduce the severity of LPS-induced lung injury by modifying mitochondrially derived reactive oxygen species, thereby reducing oxidative injury[19, 20].

Diabetic patients are often treated with ACE inhibitors because of the high incidence of cardiovascular disease. ACE inhibitors improve endothelial function in sepsis and prevent the development of pulmonary arterial hypertension and ARDS[21]. In animal models, ACE inhibitors or angiotensin receptor blockers attenuate barotrauma-induced lung inflammation and apoptosis and reduce the fibro proliferative response after bleomycin-induced lung injury [22].

Hydroxymethylglutaryl-CoA reductase inhibitors are also commonly used for dyslipidemia in diabetic patients. Statin use has been associated with reduced mortality in hospitalized patients with community-acquired pneumonia, a leading cause of ARDS[23].

4. Conclusions

In conclusion, more and more studies prove that the lung is the target organ of diabetes damage, lung injury caused by diabetes is more and more attention, but research on the mechanism of diabetic lung injury is still not very clear, so in-depth research on diabetic lung injury, further explore the mechanism of diabetic lung injury is of great significance.

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