THE ROLE OF KLOTHO PROTEIN IN THE INTERRELATION BETWEEN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND DIABETES MELLITUS: PATHOPHYSIOLOGICAL AND CLINICAL INSIGHTS

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Abstract. Chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) are prevalent chronic conditions that frequently coexist and share overlapping molecular mechanisms, including oxidative stress, inflammation, and accelerated cellular aging. The anti-aging protein Klotho plays a pivotal role in regulating metabolic homeostasis, vascular integrity, and pulmonary function. This review summarizes current knowledge of the pathophysiological interplay between COPD and DM, highlighting the contribution of Klotho deficiency to disease progression and exploring potential clinical and therapeutic implications. Recent regional and international studies support the relevance of Klotho as both a biomarker and a therapeutic target in multimorbid patients.

Keywords: Klotho protein; chronic obstructive pulmonary disease; diabetes mellitus; oxidative stress; inflammation; renal dysfunction; metabolic syndrome

Introduction. Chronic obstructive pulmonary disease and diabetes mellitus are two of the most significant chronic illnesses worldwide, often coexisting in the

same patient population. Both conditions are associated with systemic inflammation, endothelial dysfunction, and increased oxidative stress, which contribute to the progression of organ damage (1,2).

The Klotho protein, known for its anti-aging and protective effects, regulates calcium-phosphate metabolism, insulin/IGF-1 signaling, and antioxidant defenses. Reduced Klotho levels have been observed in patients with COPD and DM, suggesting a shared pathophysiological mechanism that links pulmonary and metabolic dysfunction (3,4).

Pathophysiological role of Klotho protein. Klotho exists in membrane-bound and soluble forms. It exerts anti-inflammatory, anti-fibrotic, and antioxidant effects. In pulmonary tissues, Klotho protects alveolar epithelial cells from oxidative injury, inhibits transforming growth factor-β (TGF-β) signaling, and reduces apoptosis of lung parenchyma (5). In metabolic disorders such as diabetes, Klotho deficiency contributes to insulin resistance, endothelial dysfunction, and microvascular complications. This deficiency correlates with increased oxidative stress and inflammation, establishing a common pathogenic pathway between COPD and DM (3,4).

Klotho also interacts with renal function, regulating phosphate homeostasis and mitigating vascular calcification. Its deficiency in diabetic patients accelerates kidney injury, creating a link between renal dysfunction and pulmonary disease. These mechanisms underscore the systemic relevance of Klotho in multimorbid patients.

Interrelation between COPD and diabetes mellitus. The coexistence of COPD and DM exacerbates oxidative stress, systemic inflammation, and hypoxia-related tissue injury. Chronic hyperglycemia enhances protein glycation, increasing reactive oxygen species and reducing Klotho expression (2). Similarly, chronic hypoxemia in COPD promotes inflammatory cytokine release (IL-6, TNF-α), which further suppresses Klotho expression in both pulmonary

and renal tissues. This forms a vicious cycle where Klotho deficiency accelerates tissue damage, fibrosis, and metabolic dysregulation (3,4).

Clinically, patients with both COPD and DM experience accelerated progression of renal impairment, worsened pulmonary function, and increased cardiovascular risk. Measuring circulating Klotho levels may serve as a potential biomarker for disease severity and progression in these patients (5).

Clinical and therapeutic perspectives. Klotho as a biomarker: Circulating Klotho concentration is emerging as a non-invasive indicator of systemic oxidative stress, endothelial dysfunction, and disease severity in both COPD and DM (3,5,8). Regular monitoring could aid early detection of patients at risk for multi-organ complications.

Therapeutic implications: Experimental and clinical data suggest that Klotho-targeted interventions may mitigate tissue damage. Approaches include:

Administration of recombinant soluble Klotho. RAAS inhibitors and angiotensin II receptor blockers, which upregulate endogenous Klotho expression

Vitamin D analogues with protective metabolic effects

Lifestyle modifications and antioxidant therapies to enhance Klotho bioavailability

Addressing comorbid conditions such as anemia, obesity, and renal dysfunction may further improve outcomes in patients with COPD and DM, complementing Klotho-focused strategies (6,7,9,10).

Conclusion. The Klotho protein represents a crucial molecular link between chronic obstructive pulmonary disease and diabetes mellitus. Its deficiency contributes to oxidative stress, inflammation, endothelial dysfunction, and metabolic dysregulation, unifying pulmonary and systemic complications.

Integrating Klotho measurement into clinical practice could enhance early diagnosis, risk stratification, and personalized treatment strategies. Therapeutic interventions aimed at restoring Klotho levels hold promise for slowing disease progression and improving quality of life in multimorbid patients. Further interdisciplinary studies, including regional research, are warranted to validate its clinical utility.

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