REVIEW

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UNRAVELING THE GENETIC BACKGROUND OF CACHEXIA IN COPD: A PERSPECTIVE OVERVIEW

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Abstract. *Chronic obstructive pulmonary disease (COPD) is a multifactorial disorder influenced not only by environmental exposure but also by genetic susceptibility. Recent advances in molecular genetics have enabled the identification of many candidate genes and genome-wide associations contributing to COPD development and its systemic manifestations. Cachexia in COPD is a syndrome that is associated with increased protein catabolism, severe weight loss, and reduction of muscle and adipose mass. The imbalance between protein synthesis and degradation, impaired skeletal muscle regeneration, and inflammatory activation are central mechanisms in its pathogenesis. The loss of muscle mass can be affected by mechanisms that participate in the balance between protein synthesis and protein breakdown. Thus, the impaired ability to regenerate skeletal muscle mass might contribute to the reduction of muscle mass in COPD and cachexia. Cachexia in these patients drastically increases treatment cost. Several genetic factors have demonstrated a significant association with both COPD and cachexia. Subjects with alpha-1-antitrypsin deficiency (SERPINA1) are at increased risk of developing both conditions. Early candidate gene studies have implicated ACE, bradykinin receptor, vitamin D receptor, secretory phospholipase A2, and inflammatory cytokines (IL-1 β, IL-6, TNF) in muscle loss and systemic inflammation. More recent GWAS and transcriptomic analyses have identified associations with EFNA2, BAIAP2, FTO, NEB, TPM1, and TPM2, highlighting molecular pathways involved in muscle remodeling, regeneration, and hypoxia response. The aim of this review is to summarize current evidence on the genetic factors contributing to cachexia in COPD, integrating findings from candidate gene studies and genome-wide analyses, and to discuss their potential biological and clinical implications.*

Key words: *COPD, cachexia, muscle mass reduction, genetic factors*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disorder associated with chronic respiratory symptoms and limitations of airflow. Symptoms include dyspnea (progressive over time, persistent and worsening with exercise), chronic or intermittent cough, sputum production, and frequent exacerbations. These symptoms may be the result of abnormalities in the airways – bronchitis,

bronchiolitis, or of abnormalities in the alveoli – emphysema. The ultimate effect is persistent, and often progressive, obstruction of the airflow. COPD is currently defined as a diverse group of disorders, with different risk factors and clinical courses [1]. The disease is currently the third leading cause of death around the world, and in 2019 has resulted in 3.23 million deaths [2, 3]. Although smoking is the most significant risk factor for the development of COPD, some data indicate that not all smokers progress to the disease, and the rate of progression in the impairment of pulmonary function varies among smokers [4].

Associative assessment of genetic variations has been used to compare allele and genotype frequencies between COPD patients and controls [5]. Limitations in many of these studies include small cohort size, various inclusion criteria, and inadequate statistical assessment of the results. In recent years, the main focus in studying the genetic etiology of COPD is on GWAS (Genome-wide association study), a method that has allowed for the discovery of not only frequent, but also rare genetic variations associated with COPD development [6].

Accumulating data indicate the role of genetic factors in the etiology of COPD [5, 6, 7, 8]. Recent GWAS have identified several genome loci associated with predisposition to COPD. Despite these observations, many hereditary factors linked with the disease remain unclear. This might be due to the heterogeneous phenotypic presentation of the disease [9]. Some authors observe COPD as a syndrome with various subtypes, with different biological mechanisms [10]. It has been suggested that the cumulative effect of some frequent and various rare genetic variants may provide insight into the diversity of phenotypes linked to COPD [11].

COPD and cachexia

Although COPD diagnosis is mainly based on changes in pulmonary function, it is also associated with other characteristics, such as significant weight loss (cachexia). This comorbidity affects quality of life and increases mortality risk [12, 13, 14]. A recent Bulgarian study reported a two-year mortality rate of 11.8% among hospitalized COPD patients, which increases to 17.5% in individuals with frequent exacerbations and 42.9% in those with low BMI (< 18.5 kg/m²). These findings emphasize cachexia as a major predictor of adverse outcomes and mortality in COPD [15]. Cachexia in COPD is a syndrome associated with increased protein catabolism and severe weight loss, namely, reduction of muscle mass and adipose mass. Although cachexia is mainly linked to oncologic diseases, existing data indicate that cachexia occurs 1.4 times more often in patients with COPD than in those with cancer [16].

Cachexia is defined as weight loss, mainly due to muscle mass reduction, with or without reduction in adipose mass, in patients with chronic disorders [17]. Its definition includes weight loss, more than 5% in the last 12 months or low BMI (BMI < 20) associated with 3 to 5 of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index (FFMI), elevated inflammatory markers (CRP, IL-6, etc.), anemia, or low serum albumin [17]. Additionally, COPD patients with cachexia display increased resistance to growth hormone action, compared to those without cachexia [18, 19]. Data regarding the presence of insulin resistance in these patients is still contradictory [20]. Cachexia in COPD patients is associated with a greater probability of depression, but not of anxiety [21, 22, 23].

Loss of muscle mass (the dominating mechanism for weight reduction in cachexia) can be affected by mechanisms that participate in the balance between protein synthesis and protein breakdown. Additionally, the impaired ability to regenerate skeletal muscle mass may contribute to the reduction of muscle mass in COPD and cachexia [18]. The active tripeptide glycine-histidine-lysine has an important role in this process. Its level in body fluids is reduced in patients with COPD, particularly among smokers. Glycine-histidine-lysine levels are associated with the amount of preserved muscle mass. Exogenous administration of glycyl-L-histidyl-L-lysine-Cu2+ in the cigarette-smoking [CS]-exposure mouse model is shown to have a beneficial effect on muscle mass and may exhibit a protective function against cigarette smoking-induced skeletal muscle dysfunction [24]. In COPD and cachexia, the loss of muscle mass is also associated with a shift in the ratio between slow muscle fibers (type I) and fast muscle fibers (type II), with type IIx fibers > 29% [25]. Other authors accept the cut-off criteria for altered ratio to be lower in males > 22% type IIx/IIax fibres and in females > 12% type IIx/IIax fibres [26]. This remodeling is triggered by external stimuli, which activate intracellular signal pathways in muscle cells [27].

In Europe, approximately 1.4 million patients have cachexia, and their risk of complications is 2 to 3 times higher compared to patients with normal BMI [13, 28, 29, 30, 31]. Beyond its association with mortality, cachexia also contributes to a significant reduction in exercise capacity – one of the most disabling systemic effects of COPD. In a recent study on stable COPD patients, baseline measurements showed decreased muscle mass (28.8 ± 2.43%) and markedly limited exercise performance, while after a two-month combined upper- and lower-limb training

program, maximal oxygen uptake (VO_2 max) significantly improved ($p < 0.001$), whereas muscle mass increased only slightly and without statistical significance [32]. These observations suggest that functional adaptation may precede measurable structural recovery and highlight the potential of rehabilitation to improve physical performance even in patients with advanced muscle wasting [33]. The variability in response to exercise likely reflects individual genetic and metabolic susceptibility, involving pathways that regulate muscle plasticity, mitochondrial function, and inflammatory signaling – processes in which different genetic variants may play a key role.

Despite the provided definitions of cachexia from several international task groups focused on chronic complications and cancer, diagnostics and treatment of this condition associated with COPD is still not included in the systematic approach for the disorder. This leads to an underestimation of the condition and suboptimal treatment of cachexia in actual clinical practice. A better understanding of the factors leading to cachexia in COPD is needed in order to create more effective strategies for prevention and treatment. This would not only benefit patients but would also spare significant costs for healthcare systems [17, 34, 35]. According to a recent retrospective study, including 5,484,103 hospitalizations during the period 2004 to 2019, cachexia is underreported in regular clinical practice. Also, there is an increasing trend – prevalence of cachexia for the studied period increased steadily from 1.2% to 1.9%, mainly among patients with cancer and patients with COPD [36].

Cachexia in COPD and genetic factors

Genetic predisposition to COPD and/or smoking has been observed in monogenic and complex genetic patterns [37, 38]. Subjects with a deficit for alpha-1-antitrypsin (caused by genetic variation in SERPINA1) are at a higher risk of development of both COPD and cachexia. It has been observed in clinical practice that 96% of the patients with this deficit are homozygous carriers of the Glu342Lys variant (also called variant Z), which expresses a protease inhibitory genotype ZZ (PiZZ). The largest study in Europe thus far (including patients from 20 countries) demonstrated a PiZZ/COPD ratio ranging from 0.08 to 0.24% [39]. Bulgaria was not among the countries included in the study, which highlights the need for the introduction of such testing among risk groups. Despite the tests available for SERPINA1 mutations, most patients with this deficit remain undiagnosed [40]. In a recent study conducted in the United Kingdom, including 458,164 European-ancestry participants in the UK Biobank, only 6.4% of the carriers of the PiZZ genotype have been diagnosed with alpha-1-antitrypsin deficiency. These patients have a higher risk of progression of obstruction in the airways, a higher probability of cachexia, and, subsequently, a higher mortality risk [41].

One of the challenges in the identification of the genetic predictors of cachexia in COPD is the weak to moderate effect of many of the genetic variants, which indicates the need for the evaluation of many COPD patients with and without cachexia. For this reason, the first genetic studies focused on genes that had not been phenotypically identified for cachexia. Some of them are linked with the characteristics of cachexia in COPD, such as angiotensin-converting enzyme, bradykinin receptor, vitamin D receptor, and secretory phospholipase A2. Others are responsible for the initiation of the inflammatory cascade – interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [42, 43, 44, 45]. The first GWAS for weight reduction among 4,308 patients with COPD identified significant associations with EFNA2 and BAIAP2 [46].

The EFNA2 gene encodes the membrane-linked protein ephrin-A2. The ephrins interact with Eph receptors through contact-dependent intercellular signalization that regulates homeostasis and development in various tissues, including the muscles [47, 48].

The BAIAP2 gene encodes a 53 kD insulin receptor substrate (IRSp53), an adaptation protein known for its role in the modulation of actin and membrane protrusions during intracellular signalization [49]. As previously mentioned, impaired regeneration of skeletal muscles is one of the mechanisms that contributes to loss of muscle mass in cachexia. IRSp53 can act as a negative regulator of myogenic differentiation, thus influencing the development of skeletal muscles and their regeneration [50]. The exact role of IRSp53 in COPD still remains unclear [50]. Dysregulation of IRSp53, which contributes to impaired ability for skeletal muscle regeneration, is among the possible hypotheses. Additionally, it has been proven that BAIAP2 participates in Rho-signalization, which provides an important link between the transduction of external stress signals and the intracellular signaling pathways that control genes involved in the maintenance of muscle function [51, 52].

At the single variant level, only the rs35368512 variant, intergenic to GRXCR1 and LINC02383, was associated with weight loss, but only among African American patients with COPD. This study has implied an integrative approach for the evaluation of the main proteomic network and has helped observe that gene variants linked with weight loss in COPD can influence muscle regeneration and tissue remodeling. Yet, a greater sample size is necessary, which will

include patients from different populations, both with and without cachexia [46].

An association between sarcopenia in COPD and genetic polymorphisms of FTO and AC090771.2 was observed in independent cohorts. Knockdown of FTO in murine myotubes caused molecular phenotypes consistent with senescence, which was exacerbated by hypoxia, a common condition in COPD. This genetic variation may interact with hypoxia, contributing to varying severity of sarcopenia and skeletal muscle molecular senescence phenotypes in COPD [53].

In a study of myofiber transcripts associated with abnormal myofiber proportion, twenty-nine transcripts were associated with abnormal myofiber proportions in COPD cohorts, with the upregulated NEB, TPM1, and TPM2 genes exhibiting the largest differences [26]. The NEB gene encodes nebulin, a protein associated with actin filaments in skeletal muscles, with an important role in the regulation of their length, particularly contractile regulation [54]. No other data for NEB in patients with COPD is available currently. The gene TPM1 encodes the protein alpha-tropomyosin, and the gene TPM2 encodes beta-tropomyosin. Tropomyosins are among the main regulators in the mechanism of muscle contraction [55]. Upregulation of TPM1 has been reported to have a protective effect against oxidative stress-induced degradation of the actin cytoskeleton and cell death in alveolar epithelial cells [56]. Upregulation of TPM1 in myocytes in patients with COPD has not been reported in other studies thus far. No other study to date has reported data about TPM2 in patients with COPD. The protein products (tropomyosins) have been evaluated in the diaphragm of COPD patients – in this case, COPD patients showed higher percentages of the slow isoforms of myosin light chains, troponins, and tropomyosin compared to healthy controls [57].

CONCLUSIONS

Effective management of COPD requires an integrative approach that addresses both pulmonary dysfunction and systemic complications such as cachexia. Underestimation of this condition contributes to impaired quality of life, higher hospitalization rates, and increased mortality. Incorporating genetic evaluation into clinical practice – particularly the assessment of variants influencing muscle degeneration, inflammation, and hypoxia response - may allow earlier identification of patients at risk of developing cachexia and facilitate more personalized treatment strategies.

Future research should focus on combining genomic, transcriptomic, and epigenetic profiling with clinical and metabolic parameters to clarify the molecular mechanisms linking COPD and cachexia. Such integrative analyses could support the development of biomarkers for early detection, molecular targets for therapy, and individualized rehabilitation programs aimed at muscle preservation and improved physical performance. Ultimately, recognizing and addressing the genetic background of cachexia in COPD will not only advance precision medicine but also enhance patient outcomes, reduce disease burden, and improve long-term prognosis.

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