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THE BENEFITS OF SMOKING CESSATION ON PATIENTS WITH COPD – A NARRATIVE REVIEW

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major healthcare problem and an important cause of mortality worldwide, causing 3,23 million deaths in 2019, 90% of COPD deaths in those under the age of 70 in low and middle-income countries according to WHO (World Health Organization). COPD is the third leading cause of death globally, with 24% of patients dying within five years of diagnosis[1]. Smoking is the most common risk factor for COPD, as tobacco smoke contains a large number of toxic substances that are both the cause of COPD and the main factor implicated in the progression of the disease[2].

This narrative review aims to provide scientific help to healthcare professionals to understand the importance of focusing on smoking cessation amongst patients with COPD as the main treatment method, besides pharmacological therapy. The global burden of COPD mortality must be addressed through efforts to reduce exposure to risk factors, assess individual patient risk, and use treatments that lower mortality. In countries that have adopted comprehensive strategies for prevention and treatment, COPD-related mortality rates have declined. The latest research points out the importance of smoking cessation in the prognosis and quality of life among COPD patients.

Keywords: *Tobacco smoking, chronic obstructive pulmonary disease, COPD, smoking cessation.*

Rezumat

Boala pulmonară obstructivă cronică (BPOC) este o problemă majoră de asistență medicală și o cauză importantă de mortalitate la nivel mondial, provocând 3,23 milioane de decese în 2019, 90% din decesele BPOC la cei sub 70 de ani în țările cu venituri mici și medii, conform OMS (Organizația Mondială a Sănătății). BPOC este a treia cauză de deces la nivel global, 24% dintre

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pacienți decedând în decurs de cinci ani de la diagnosticare. Fumatul este cel mai frecvent factor de risc pentru BPOC, deoarece fumul de tutun conține un număr mare de substanțe toxice care sunt atât cauza BPOC, cât și principalul factor implicat în progresia bolii.

Această revizuire narativă își propune să ofere ajutor științific profesioniștilor din domeniul sănătății pentru a înțelege importanța concentrării asupra renunțării la fumat în rândul pacienților cu BPOC ca metodă principală de tratament, pe lângă terapia farmacologică. Povara globală a mortalității BPOC trebuie abordată prin eforturi de reducere a expunerii la factorii de risc, evaluarea riscului individual al pacientului și utilizarea tratamentelor care scad mortalitatea. În țările care au adoptat strategii cuprinzătoare de prevenire și tratament, ratele mortalității legate de BPOC au scăzut. Cele mai recente cercetări subliniază importanța renunțării la fumat în prognosticul și calitatea vieții în rândul pacienților cu BPOC.

Cuvinte cheie: *fumatul de tutun, boală pulmonară obstructivă cronică, BPOC, renunțarea la fumat.*

Introduction

COPD is a chronic, incurable, and life-threatening respiratory disease caused by various factors. It is a major cause of morbidity and mortality in economically developed nations and is increasingly emerging as a significant health concern in developing countries[3]. COPD is characterized by chronic airflow limitation, that is not entirely reversible, generally progressive, and associated with an inflammatory pulmonary response to toxic particles and gases[4].

COPD is a widespread disease, affecting 10% of the global population, and according to the evaluations performed by WHO, COPD will become the third leading cause of death by 2030[5].

There are many risk factors for developing COPD, and current research show that smoking, biofuels, indoor, outdoor air pollution and industrial dust are the major environmental risk factors. However, the most important cause of COPD remains cigarette smoking[3].

The 2023 WHO report on the global tobacco epidemic showed that tobacco consumption killed an astounding 8.7 million people every year. And even more shocking is that 1.3 million of these deaths are among people who do not use tobacco, including infants and children. In particular, women and children

are vulnerable to second-hand smoke exposure[6].

Although passive smoking is also related to developing COPD[3], active smoking has been associated with COPD severity, patient's quality of life and comorbidities[4]. Cigarette smokers have a higher prevalence of respiratory symptoms, abnormal lung function, a greater annual decline in FEV1 (forced expiratory volume in 1 s) and a great mortality rate compared with non-smokers[7].

In spite of the fact that rate of cigarette smoking is decreasing in several countries, it remains a serious threat to public health worldwide, particularly in South-East Asia as well as in Eastern Europe with the world`s largest number of smokers. The WHO estimates that by 2050 there will be 1,5 billion smokers globally[8].

Even though smoking is the primary cause of COPD, it does not lead to COPD in all smokers, as in the study conducted by Fletcher et al., airway obstruction was observed in 12% of the moderate smokers and 26% of the heavy smokers[9].

Also, in an umbrella review conducted by Holtjer and all. stated that active smoking, as compared to nonsmokers, is the main risk factor for COPD[10].

COPD self-management is an essential component of COPD management behaviors such as quitting smoking, medication adherence, correct inhaler use, healthy diet and physical activity[11].

The importance of smoking cessation cannot be understated, as many studies showed the benefits almost all smokers have regardless the age of quitting or the cumulative amount of tobacco exposure. Whereas the reduction risk is rapid for others diseases such as cardiovascular disease, for cancer and COPD the reduction risk is more gradual, indicating the importance of smoking cessation at a young age in life to maintain respiratory health[12].

Physiopathology

COPD is a disease that is characterized by progressive airflow limitation that is not fully reversible and it is associated with an unusual inflammatory response of the lungs to noxious particles and gases[13].

COPD is a complex obstructive illness that includes chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, emphysema with expansion of airspaces and destruction of lung parenchyma, loss of lung elasticity and closure of small airways[13], but also an increased mucus secretion, plasma leakage and expansion of submucous glands[9].

The primary protective barrier against inhaled toxic substances and microbes is considered to be the bronchial epithelium, as it is playing a vital role in maintaining tissue homeostasis. Any disruption in homeostasis accentuates the inflammatory response and repair process[14].

Irritants in the airways activate various cells that produce and release chemotactic factors that attract additional inflammatory cells[9].

Inhalation of tobacco smoke is a powerful inducer of inflammation both in respiratory tract but also systemically. Tobacco smoke induces mucosal inflammation, heightens oxidative stress and fibrinogen concentration, increases hs-CRP (high-sensitivity C-reactive protein) and expression of inflammatory cytokines[15]. As a result of accumulation of inflammatory mucous exudates in the lumen and an increase in the thickness of the bronchial wall, the inflammatory process persists in those who continue to smoke, despite smoking cessation and progressively worsens over time[16]. Several inflammatory

cells types are involved in the physiopathology of COPD, including macrophages, neutrophils and T-cells[13], along with adaptive inflammatory immune cells like CD4, CD8, and B lymphocytes and sometimes eosinophils[16].

Neutrophils are the inflammatory cells that play a central role in the pathogenesis of COPD, sputum and blood neutrophilia is an important hallmark of COPD and a marker of COPD severity[17].

Cigarette smoke reduces the deformability of neutrophil granulocytes which may explain the slow wash out rate of these inflammatory cells from the lungs in smokers[9]. Their accumulation in COPD lungs are significantly increased which is correlated with disease severity and their secreted products have been shown to all major pathological aspects of the condition[18]. Neutrophils release a serine proteases including neutrophil elastases (NE), matrix metalloproteinase (MMP), myeloperoxidase (MPO), all of which have as final result alveolar destruction[17]. Neutrophils from COPD patients have been shown to secrete increased amounts of ROS (reactive oxygen species) both spontaneously and following stimulation[18].

Alveolar macrophages are also key players in airway inflammation in COPD. These cells release a large variety of chemokines and cytokines such as tumor necrosis factor-alpha (TNF-alfa). Alveolar macrophages also produce ROS, MMPs and cathepsins, which contribute to alveolar damage and induce fibrosis mediators such as TGF-beta1 (transforming growth factor-beta-1) to trigger airway remodeling[19]. Macrophage can be directly activated by cigarette smoke and play a key part in sustaining the chronic inflammation in the pulmonary tissue of COPD patients[16]. Alveolar macrophages obtain by bronchoalveolar lavage (BAL) from smokers are primed to release higher amounts of ROS compared with those obtained from non-smokers[13].

In COPD, the adaptive immune system is activated, leading to infiltration of T-cells, B-cells, T-helper type 17 (Th17) cells, along with a reduction in regulatory T cells within the airways. T-lymphocytes numbers are increased in the lung parenchyma and airways of smokers compared with never smokers, regardless of COPD development. CD8 are another cells that increase more significantly than CD4 cells, and this increase in peripheral airways is linked to smoking-related airway obstruction. The number of B-cells in the lymphoid follicles is also greatly increased in advanced stages of COPD[17].

Another inflammatory cells that are correlated with COPD inflammation are eosinophils, but the role of eosinophils is less certain in COPD than in asthma. Increased numbers of eosinophils have been reported in bronchial biopsies, but also in BAL fluid during

acute exacerbation of chronic bronchitis[20].

Various inflammatory mediators are implicated in COPD, including lipids, free radicals, cytokines, chemokines and growth factors[20].

Oxidative stress (OS) also plays an important role in COPD giving the increased oxidant burden in smokers [13]. OS has important effects on both lung function and COPD pathogenesis. The most important effects on pathogenesis caused by OS are apoptosis, remodeling of the extracellular matrix, alveolar epithelial injury, mitochondrial respiration, membrane lipid peroxidation (LPO), mucus hypersecretion, and oxidative inactivation of surfactants and antiproteases[21].

In COPD patients, elevated level of OS results from environmental exposure including air pollutants and cigarette smoke, and from the elevated levels of reactive nitrogen species (RNS) and ROS released by macrophages and leukocytes during inflammation[21].

ROS play a critical role in tissue damaging and cell injury linked with numerous inflammatory pulmonary diseases including COPD [21]. Cigarette smoking contains over 1016–1017 oxidants per puff and around 4700 chemicals such as nitrogen oxides, superoxide radicals and peroxynitrite[21].

OS arises from an imbalance between reactive oxygen species production and antioxidant defense. Adequate balance is essential to prevent cellular damage[22]. Increased OS in COPD is linked to impaired antioxidant defenses[23].

Impact of smoking cessation on respiratory symptoms amongst COPD patients

As people age, their lung function typically declines, and their ability to repair lung tissue and manage baseline inflammation is reduced. The burden of COPD reaches its peak in older adults, as usually they are patients that have an important variety of comorbid conditions. Combined with the natural increase in comorbidities associated with aging, this results in a higher mortality rate for elderly individuals with COPD[24].

Many studies have examined the impact of smoking on respiratory health. The groundbreaking research by Fletcher and Peto, published in 1977, laid the foundation for our current understanding of how smoking damages lung function and highlighted the critical importance of quitting smoking[25].

The only intervention proven to slow the rate of lung function decline in COPD patients is smoking cessation and is proved that also smoking cessation reduces mortality. From a public health standpoint, smoking cessation is the most effective treatment for COPD and leads to a reduction in symptoms[26].

The Lung Health Study showed that smoking cessation interventions led to a reduction in symptoms such as dyspnea, cough, sputum production, and wheezing. In the study conducted by David H. Au and all. It is shown that individuals who quit smoking earlier in the course of their disease may have milder symptoms and are therefore more likely to experience grater benefits from smoking cessation[26].

Alongside the well-established phenotypes of bronchitis and emphysema, clinicians also identify the phenotype of COPD with frequent exacerbations [25]. Exacerbations in COPD, are known to accelerate the decline in lung function, leading to reduced physical activity, diminished quality of life, and an increased risk of death[27].

There are many factors that lead to COPD exacerbation, but an important role is tobacco smoking. COPD patients who continue to smoke have a high rate of exacerbations that necessitate hospitalization. On the other

hand, quitting smoking is linked to a lower risk of exacerbations, with the magnitude of risk reduction correlating with the length of time since quitting[26].

COPD exacerbations are characterized by worsening of respiratory symptoms, such as coughing, shortness of breath, increased sputum production and can be triggered by viral or bacterial infection. It is essential to recognize that COPD exacerbations are closely linked to the microbiota in the respiratory tract, microbiota which is disrupted by smoking[28].

There are some studies that discovered that patients with severe COPD have a higher abundance of species from the Lactobacillus genus compared to those with milder or no COPD. Other research has reported increased levels of Veillonella, Streptococcus, and Granulicatella, with the latter especially elevated in late-stage cancer. This dysbiosis, or the abnormal imbalance of bacterial species, is believed to raise levels of ROS associated with DNA damage in the lungs[29].

There have been some significant studies in the latest years that highlighted the importance of cessation smoking among COPD patients. Godtfresen et al. conducted a prospective cohort study involving 19,709 individuals from general population to assess the risk of hospitalization for COPD following whether complete smoking cessation or a reduction in Tabaco smoking over a 14.4 year period. The risk of hospitalization was lower in patients with complete cessation compared to continued smoking (RR = 0.57; 95% CI: 0.33–0.99. On the other side, merely reducing smoking did not show a significant reduction in hospitalization risk compared to persistent smoking (RR = 0.93; 95% CI: 0.73–1.18)[30].

Kanner at al. studied 5,887 participants from the Lung Health Study 1, focusing on current smokers aged 35 to 60 years with mild to moderate COPD. Two groups were given either inhaled ipratropium bromide or a placebo, along with supportive interventions, while the third group received only smoking cessation advice. After five years, the prevalence of respiratory symptoms was significantly reduced in the intervention groups compared to the control group ($p < 0.0001$). Those who continued smoking had a higher prevalence of symptoms compared to those who quit ($p < 0.0001$), with symptom improvement apparent within the first year of smoking cessation[30].

Another significant study was conducted by Tonnesen et al., involving a multicenter trial with 370 COPD patients of varying disease severity, aimed at supporting smoking cessation. The study assessed patients using the Saint George's Respiratory Questionnaire at baseline, six months, and twelve months. Participants who quit smoking or reduced their consumption showed improvements in various questionnaire scores, except for the

'Activity' dimension, which remained unchanged among those who only reduced their smoking[31].

Willemese and col. highlight that in both cross-sectional studies and longitudinal studies is suggested improvement of the respiratory symptoms after smoking cessation, as the most intermitent symptoms (cough, phlegm and wheeze) decrease within 1–2 months after smoking cessation. After smoking cessation the prevalence of cough and wheezing reduces to levels comparable to those of nonsmokers, but the prevalence of phlegm remains slightly elevated[32].

On the other hand, three studies, with smoking cessation periods ranging from 2–6 weeks to 1–12 years, found no change in the prevalence of dyspnea following smoking cessation[32].

In a study conducted by Yong Liu and col., in which the data are collected from 4,135 adults aged 45 and older, years with a history of smoking, showed that patients with COPD that continued to smoke were more likely to have a productive cough, that is consistent with chronic bronchitis. This condition is primarily due to excessive inflammation and hypersecretion of mucus secondary to smoking tobacco products use. Another important conclusion emerged from this study is that the difference in the frequency of dyspnea between current and former smokers was less pronounced[33].

Does quitting smoking improves lung function?

Chronic airflow obstruction, identified through spirometry, is the hallmark of COPD. Maximum expiratory flow is determined by resistance in small airways (cm H_2O/L/s) and the lung's elastic recoil, which drives expiratory flow (L/cm H_2O). The interaction of these factors, called the time constant, dictates how quickly the lungs fill and empty. In healthy lungs, this time constant is consistent across breathing rates. However, conditions like emphysema, which increase lung compliance or airway resistance, prolong lung emptying. Spirometry diagnoses fixed airflow limitation by measuring FEV1 and the FEV1/FVC (Forced vital capacity) ratio after bronchodilator use[34].

Quitting smoking presents a crucial opportunity to prevent COPD, as it slows the decline in FEV1, thereby preventing smoke-related respiratory impairment[35]. Additionally, smoking cessation helps prevent other smoking-related lung diseases by positively influencing key inflammatory and remodeling processes in the lungs[36].

Spirometry is essential for assessing airflow limitation, particularly by measuring FEV1. A low FEV1 is predictive of not only an accelerated decline in lung function but also higher rates of morbidity and mortality [37]. Since lung function naturally decreases over time, preventing smoking-related illnesses should begin early in life, though many smoking cessation programs face high relapse rates[38].

Respiratory symptoms alone do not predict changes in lung function, but smokers with airflow obstruction benefit from quitting, regardless of past heavy smoking, advanced age, poor baseline lung function, or airway hyperresponsiveness[38].

About 30% of smokers may not exhibit chronic symptoms or abnormal lung function; however, even these "healthy smokers" experience subtle changes in lung morphology, inflammation, and function. Smoking invariably impacts the lungs, though the severity and extent of these changes vary among individuals[32]. A study by Dhariwal J et al. explored the relationship between smoking and lung function, showing that COPD patients who quit smoking experienced a

significant but temporary improvement in FEV1 at 6 weeks (184 mL), which persisted somewhat at 12 weeks (81 mL) and was partially maintained after one year. Additionally, both COPD patients who quit smoking and those with normal spirometry who quit smoking showed improvement in lung carbon monoxide transfer factor at 6 weeks[39].

Pezzuto et al. found in their study that reducing cigarette exposure enhances airflow parameters and exercise performance in patients. Data from plethysmography and hemogasanalysis indicated a significant improvement in lung function over a short treatment period (3 months). Increases in vital capacity, FEF 25-75 (Forced Expiratory Flow 25-75%), and FEV1 were accompanied by a decrease in dyspnea index scores and reduced COHb (Carboxyhemoglobin) levels. They also noted that for mid-sized and larger airways, it takes about a year for FEV1 reductions to develop[35].

Spirometric lung age, derived from height and FEV1 using a formula introduced by Morris and Temple, was designed to simplify spirometry data and highlight the effects of smoking to smokers. While some studies have explored whether sharing spirometric lung age influences behavior, little is known about its response to intensive or partial smoking cessation. A study by Iwaoka M. et al. examined changes in lung function in smokers who achieved complete or partial cessation. They found that smokers who fully quit experienced improved lung function within 12 weeks, whereas partial cessation showed no significant short-term benefits[37].

In a systematic review of epidemiological data on smoking and the annual rate of FEV1 decline (beta), Lee PN et al. found that continuing smokers exhibit a beta over 10 mL/yr higher than never-smokers, with beta increasing proportionally to daily cigarette consumption. Ex-smokers have betas comparable to never-smokers, while quitters show only slightly elevated betas. The differences in betas between continuing smokers and quitters do not appear to vary significantly by age or sex but are more pronounced in populations with respiratory diseases compared to the general population[40].

A study by Tashkin et al. analyzed serial spirometric data to assess the sustainability of short-term lung function improvements after smoking cessation. Significant gains were observed within 9 to 12 weeks of abstinence, but these improvements were not maintained at 24 or 52 weeks. The reasons for this decline remain unclear, though substantial long-term benefits may require more than a year of cessation. This study highlights the short-term respiratory benefits of quitting smoking in COPD patients, offering motivation for smokers with COPD to pursue cessation[41].

Paul D. Scanlon et al. conducted a five-year prospective trial with 3,926 smokers with mild-to-moderate airway obstruction across 10 North American centers. Participants were assigned to smoking cessation or non-intervention groups, with annual lung function assessments. Quitters experienced a 47 mL (2%) FEV1 improvement in the first year, and their annual FEV1 decline over four years was half that of continuing smokers. Greater initial airway responsiveness and lower lung function predicted larger first-year improvements, while younger participants and women showed better outcomes overall. However, women who continued smoking had greater FEV1 decline than men[38].

The ECLIPSE study, led by Vestbo J and colleagues, tracked 2,164 COPD patients over three years with detailed assessments at baseline and multiple follow-ups. Testing included CT scans, spirometry, 6MWT (Six-Minute Walk Test), and biomarker sampling. FEV1 decline showed considerable variability, averaging 33 mL/year—lower than expected. Key contributors to faster decline were continued smoking (21 ± 3.8 mL/year), CT-defined emphysema (13 ± 4.2 mL/year), and bronchodilator reversibility (17 ± 4.2 mL/year)[42].

Smoking cessation is the most effective strategy to slow the accelerated decline in lung function and improve respiratory symptoms in smokers with COPD[41]. When counseling smokers to quit, they may argue they are too old to benefit, smoke too much to quit, or have already caused irreversible lung damage. However, studies strongly refute these claims. Heavy smokers gain the most from quitting and risk the most by continuing. Older smokers see similar benefits to younger ones in slowing lung function decline. Those with the worst lung function experience the fastest deterioration if they keep smoking, making quitting especially crucial for them[38].

An optimal smoking cessation strategy today should include a comprehensive support program, whether individual or group-based, combined with a first-line pharmacological smoking cessation agent, such as NRT (Nicotine Replacement Therapy), varenicline, or bupropion SR for three months. If relapse occurs, retreatment should be offered[43].

The value of CT for the diagnosis of smoking related comorbidities

COPD is a syndrome that includes a diverse range of conditions, all characterized by chronic airflow obstruction, with varying contributions from emphysema, small-airway disease, and chronic bronchitis. This airflow limitation is irreversible and results from different combinations of central and peripheral airway damage as well as emphysematous changes, which occur due to the destruction of alveolar structures from prolonged exposure to harmful particles or gases[44].

Among all risk factors, smoking is the primary known contributor to the development of COPD. However, the degree of chronic airflow obstruction that develops varies significantly among smokers[45]. Since not all smokers will develop COPD, predictive factors like the extent of low-attenuation areas in individuals without airway obstruction could help identify those at risk of developing the disease. For instance, a diagnosis of COPD via HRCT (High-Resolution Computed Tomography) can be made by detecting diffuse, scattered low-attenuation areas in the lung parenchyma[46]. This is crucial because stabilizing the disease through smoking cessation is a key aspect of COPD management[47].

Early diagnosis of COPD allows for earlier treatment and improved prevention of

exacerbations, which are closely tied to accelerated lung function decline, highlighting the need to avoid these events. Quantitative CT scans measuring emphysema are strong predictors of COPD, while air trapping can help identify non-emphysematous COPD. Additionally, airway wall thickness, which can be easily measured on inspiratory CT scans, serves as a valuable biomarker for diagnosing COPD and is linked to airflow obstruction[48].

Firdaus Mohamed Hoesein et al. investigated the impact of emphysema on lung function decline in male current and former heavy smokers. Participants, recruited from a lung cancer (LC) screening trial, underwent CT scans and spirometry at baseline and after three years. The study revealed that a greater extent of baseline low-attenuation areas was linked to a more pronounced decline in lung function, highlighting the role of smoking-related emphysema in disease progression[47].

Smokers with interstitial abnormalities on HRCT, especially those with COPD, tend to have reduced total lung capacity[49].

Remy-Jardin et al. investigated longitudinal CT changes in smokers, comparing those who quit to those who continued smoking. In continuing smokers, lung parenchymal abnormalities, such as emphysema, ground-glass attenuation, and ill-defined micronodules, worsened over time. The study concluded that individuals with emphysema or ground-glass attenuation on initial scans experienced significantly faster lung function decline than those with normal CT findings[50]. Another important study focused on the primary sites of obstruction in COPD patients. John E. McDonough et al. identified small airways (<2 mm in diameter) as the primary sites of obstruction in COPD. Using multidetector CT, they compared small airway counts in COPD patients at different stages, transplanted lungs, and donor lungs. Their findings showed a reduced number of small airways in mild COPD (GOLD 1), with further loss in severe COPD (GOLD 3–4). They concluded that narrowing and loss of small airways precede emphysematous destruction, contributing to increased peripheral airway resistance in COPD[51].

Micronodules are another feature that can be present in a smoker's lungs. Since the introduction of helical computed tomography in the early 1990s and multi-detector row CT in the late 1990s, identifying nodules as small as 1–2 mm in diameter has become routine. Nearly 20% of smokers who undergo thin-section CT scans have lung nodules, most of which are smaller than 7 mm in diameter. The Fleischner Society committee on CT nomenclature defines a nodule as a “round opacity, with well-defined margins and no greater than 3 cm in maximum diameter.” Eliana Maci et al. concluded that smoking cessation reduces the number and size of

lung nodules and improves lung function[36]. In a study by Dhariwal J et al., the effects of smoking cessation were examined in a group of asymptomatic smokers with moderate to severe COPD on spirometry and in a group with normal spirometry. They assessed the impact of smoking cessation by measuring spirometric lung volume and gas transfer criteria.

These lung function parameters were monitored in relation to the presence of emphysema, micronodules, and ground-glass opacities on HRCT scans. Their study concluded that spirometry only detects a fraction of patients with smoking-associated lung lesions. Moreover, they found that while smoking cessation does not improve emphysema, it does reduce the presence of micronodules detectable on HRCT scans[39].

Impact of smoking cessation on COPD complication.

Cardiovascular disease

Smoking is one of the modifiable risk factors for many chronic diseases, such as cardiovascular disease (CVD), cancer, chronic obstructive lung disease, asthma, and diabetes[52].

CVDs, such as ischemic heart disease, heart failure, and cardiac arrhythmias, are prevalent comorbidities in COPD patients, alongside diabetes and LC. In COPD patients, CVDs account for up to 30% of all-cause mortality [53]. Cigarette smoking is a leading cause of CVD, responsible for approximately 140,000 premature deaths annually. Epidemiological evidence strongly links smoking to negative outcomes in patients with existing coronary heart disease, with those who continue to smoke after a myocardial infarction facing a 50% higher risk of recurrent coronary events compared to nonsmokers[54].

Smoking not only acts as an independent risk factor but also exacerbates other major risk factors[34].

It negatively impacts various coronary heart disease (CHD) risk factors, including increasing cholesterol, triglycerides, low-density lipoprotein cholesterol, and fasting blood glucose, while decreasing high-density lipoprotein cholesterol and endurance capacity. Additionally, smoking contributes to earlier natural menopause, higher erythrocyte and leukocyte counts, and elevated fibrinogen levels[55]. Smoking alone doubles the risk of CVD, and when combined with another major risk factor, the risk increases up to fourfold[34]. Additionally, it more than doubles the risk of various forms of CVD, including coronary heart disease, ischemic stroke, peripheral arterial disease (PAD), and abdominal aortic aneurysm (AAA).

Thus, smoking cessation is a fundamental strategy for improving cardiovascular health[56]. The acute pro-thrombotic, pro-adrenergic, and pro-inflammatory properties of smoking are thought to underlie smoking-associated atherosclerosis and cardiovascular disease [57]. Smoking triggers an immunological response to vascular injury, leading to oxidative stress, lipid peroxidation, endothelial cell dysfunction, and foam cell proliferation in the tunica media. A study by Arvind Bakhru et al. found that inflammatory markers, which are more accurate indicators of atherosclerotic disease, returned to baseline levels within five years of smoking cessation[58]. The age at which significant excess risk due to cigarette smoking begins varies by disease. For individuals under 45 years old, CHD is the primary cause of increased mortality linked to smoking. The excess mortality rate from LC rises sharply after age 50, while the elevated death rates from COPD are mostly observed in the seventh and eighth decades of life [34].

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Cardiovascular risks generally increase with the number of cigarettes smoked daily, but the relationship is complex[59]. Even low levels of tobacco exposure, such as a few cigarettes per day, occasional smoking, or secondhand smoke exposure, can significantly increase the risk of cardiac events[34].

Smokers who reduce their cigarette consumption may compensate by inhaling more deeply, thereby increasing their exposure to harmful toxins. Additionally, the type of tobacco product used can distort actual exposure levels; for example, "low tar" and "low nicotine" cigarettes are smoked differently than regular ones, and cigar smokers typically do not inhale. Importantly, the risk of coronary heart disease triples even with minimal smoking (1-4 cigarettes per day), though the increase in risk becomes less pronounced beyond five cigarettes per day[59].

The risk of myocardial infarction (MI) and death from CHD is lower among former smokers than among those who continue to smoke, even when data is adjusted for other risk factors. In asymptomatic patients, the risk of death from smoking-related heart disease decreases by nearly 50% within the first year after quitting. Among smokers with existing coronary artery disease (CAD), smoking cessation is associated with a 32% reduction in the risk of nonfatal reinfarction and a 36% reduction in mortality, making quitting smoking more effective at reducing mortality than other secondary prevention measures, such as the use of statins, aspirin, beta-blockers, or ACE inhibitors[60].

Cigarette smoking is a major cause of CHD, stroke, aortic aneurysm, and PAD. Even passive smoking increases the risk of atherosclerotic cardiovascular disease (ASCVD) by 30%, compared to an 80% increased risk in active smokers[61]. The risk is associated with both acute thrombosis of narrowed vessels and an increased degree of atherosclerosis [34]. Notably, the mortality from CVDs is higher in female smokers than in male smokers, with women showing a 25% higher risk of developing CHD than men with the same level of tobacco exposure. This increased vulnerability in women may be linked to genes involved in thrombin signaling[61].

Smoking cessation reduces the risk of cardiovascular morbidity and mortality in smokers, whether or not they have CVD. Smoking accelerates atherogenesis, causes acute cardiovascular events, and interacts synergistically with other risk factors like hyperlipidemia and diabetes. Although smoking does not directly cause hypertension, it is associated with higher blood pressure in individuals with hypertension and increases the likelihood of complications, including the progression of renal disease[34].

The extent and duration of risk reduction following smoking cessation remain uncertain. While risk declines immediately after quitting, it is unclear when, or if, the risk returns to the level of lifelong non-smokers. Some studies suggest that the risk of CHD may return to that of non-smokers within 3-5 years, while others indicate it may take up to 20 years[62].

Dobson et al. concluded that the risks decline rapidly after quitting so that ex-smokers who quit more than 3 years ago were not at greater risk than non-smokers[63]. Another study showed that a large part of the excess risk of acute MI associated with smoking diminishes within 5 years, and among light smokers there was no excess risk after 3–5 years of quitting. Although, moderate and heavy smokers still had an increased risk even 20 years after quitting [64]. These observations have led some to hypothesize that long-term exposure to tobacco smoke may cause irreversible changes in the regulation of the autonomic cardiovascular system[62].

Many studies on this topic rely on self-reported smoking status, which can lead to inaccuracies, particularly when smoking habits change during follow-up. Twardella D et al. found that 20% of patients altered their smoking status within the first year after a coronary heart disease diagnosis, suggesting that the impact of smoking cessation on long-term prognosis may be greater than previously thought. This highlights the need for ongoing support in smoking cessation and relapse prevention[65].

While some interventions have successfully reduced the number of cigarettes smoked per day, the reductions in biomarkers of exposure and cardiovascular risk factors are often not proportional, likely due to compensatory smoking and the nonlinear dose-response relationship[34]. One study examining the effects of smoking cessation drugs on blood pressure and heart rate found that these medications, whether used alone or in combination, did not influence systolic blood pressure (SBP), diastolic blood pressure (DBP), or heart rate in the observed patients[66].

Lung cancer

There are many lung diseases, that are also independently linked to tobacco smoking and often co-exist with COPD as lung cancer, pulmonary hypertension, pulmonary emboli, and sleep apnea [67]. LC has emerged as one of the primary causes of preventable deaths in recent decades. While other factors like occupational exposures, air pollution, asbestos, and radiation have also been identified as contributing causes to LC, cigarette smoking remains the main cause of the disease[68]. LC incidence varies significantly around the globe, with the highest rates found in Western countries such as the United States, Canada, and Europe, while developing countries report lower rates[69].

To understand the etiology of LC, in the 1950s were conducted the first epidemiological studies by British and American scientists that established a link between the effects of cigarette smoking on the airways and lung parenchyma and the development of LC. The results of these studies are that both the duration of smoking and the number of cigarettes smoked increased the risk of LC among smokers. Importantly, further research that was made showed that the length of time a person smoked was a stronger predictor of LC risk than the number of cigarettes consumed daily[68]. Tobacco smoking is the primary risk factor for both diseases, yet COPD itself is an independent risk factor for LC. This predisposition, supported by our understanding of the

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underlying mechanisms, suggests that LC may develop as a progression of COPD[70]. Smoking cessation is fundamental in COPD management. It is the fundamental way of stopping the progression of COPD and reducing the risk of developing LC[71].

There are several epidemiological studies that indicate that while tobacco smoke exposure accounts for over 80% of COPD and LC cases, only 10–15% of smokers develop LC, and 20–30% develop clinically significant COPD.

Also, research from the past 30 years consistently shows a strong association between reduced FEV1 (or COPD) and an increased risk of LC. Recent studies demonstrate that smokers with COPD (or reduced FEV1) have a 4- to 6-fold higher risk of developing LC compared to smokers with normal lung function or those arbitrary selected from the general population[72].

The pathophysiological links between COPD and LC have been challenging to define because of the varied responses to chronic inflammation and lung repair mechanisms. Potential shared processes include imbalance between proteases and anti-proteases, chronic inflammation, genetic predisposition epigenetic alterations, telomere shortening, mitochondrial dysfunction, premature aging, and abnormal reparative processes[73],[74].

Tobacco smoking, a common risk factor for both LC and COPD, contributes significantly in lung carcinogenesis by merging smoking-related inflammation with the presence of tobacco smoke carcinogens. Decreased mucociliary clearance could may allow carcinogens to remain in the lungs for extended periods. The lung microbiome in patients with COPD is different from that of healthy individuals and may contribute to inflammatory changes that promote LC development[73].

Numerous prospective clinical studies have revealed a notably higher incidence of LC in patients with COPD. For example, in a 5-year prospective cohort study of former and current smokers, conducted by Torres et al. found that patients with emphysema are at a higher risk of developing LC compared to those without emphysema. The risk was significantly higher for individuals with both emphysema and airway obstruction compared to individuals with neither condition[75].

A research that was based on adult participants from the US First National Health and Nutrition Examination Survey with up to 22 years of follow-up identified a connection between LC and COPD. In the study the individuals were assessed by lung function tests that classified the patients with moderate to severe obstructive lung disease at baseline if their FEV1/FVC ratio was below 0.70 and their FEV1 was less than 80% of the predicted value. During the follow-up period, 113 cases of LC (2.0%) were observed among the 5,402

participants. The proportional hazards model, showed that the presence of moderate to severe obstructive lung disease was linked with a significantly higher risk of developing LC (hazard ratio of 2.8; 95% CI: 1.8-4.4)[76].

Diabetes

Approximately 537 million adults worldwide aged 20-79 (10.5% of this age group) have diabetes. By 2030, this number is expected to reach 643 million, and by 2045, 783 million. This represents a 46% increase in diabetes cases, compared to a 20% growth in the global population during this period[77]. Diabetes mellitus (DM) is marked by chronic hyperglycemia, leading to irreversible damage to blood vessels, which in turn causes macrovascular complications (such as coronary artery disease, stroke, peripheral artery disease, and erectile dysfunction) and microvascular complications (such as retinopathy, nephropathy, and diabetic neuropathy)[8]. The growing global diabetes epidemic exacerbates the clinical and public health burden posed by tobacco use among individuals with diabetes[78]. Cigarette smoking is one of the most significant modifiable risk factors for DM[8].

Numerous clinical and experimental studies have demonstrated strong associations between cigarette smoking and the development of diabetes, impaired glycemic control, and both microvascular and macrovascular complications. The lifestyle differences between smokers and nonsmokers may also contribute to these effects[34]. However, the harmful impact of smoking on diabetes is often underrecognized. While smoking is known to reduce body weight, it is also linked to central obesity and increases inflammation and oxidative stress, which directly damages β-cell function and impairs endothelial function[52]. Evidence indicates a positive correlation between smoking and increased CVD risk among patients with diabetes[79]. Cigarette smoke exposure is associated with vascular damage, endothelial dysfunction, and activation of the blood-clotting cascade, leading to higher cardiovascular morbidity and mortality in diabetic patients compared to non-diabetics[8]. One prospective study examining the effects of smoking cessation on cardiovascular risk in diabetics found that the mortality risk was approximately 50% higher for those who had quit smoking within the last one to nine years and 25% higher for those who had quit over nine years ago, compared to lifetime nonsmokers. Although smoking cessation reduced mortality risk in diabetic individuals, the risk remained elevated for several years after quitting[34].

Experimental studies have consistently shown that smoking negatively affects glucose and lipid metabolism in individuals with or without diabetes[34]. Smokers with diabetes tend to have higher low-density lipoprotein (LDL) and triglyceride levels, and lower high-density lipoprotein (HDL) levels. Additionally, despite receiving the same treatment, smokers with diabetes exhibit poorer glycemic control compared to nonsmokers, as indicated by higher glycated hemoglobin (A1C) levels[79].

Smoking also increases the risk of developing type 2 diabetes in the general population, and it is widely acknowledged that smoking significantly raises the risk of microvascular and macrovascular complications in patients with type 2 diabetes mellitus (T2DM)[8]. This increased risk may result from direct metabolic effects alone or in combination with an unfavorable lifestyle. Studies have also shown a strong positive association between the risk of developing diabetes and higher cigarette consumption[34], with both the

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duration and amount of smoking increasing the risk of microvascular complications, while quitting smoking improves nephropathy[80].

When it comes to mortality, a study by Chi et al. revealed a synergistic relationship between smoking and diabetes, with the combined effect significantly increasing the risk of death compared to either condition alone [81]. Overweight or obesity are the strongest predictors of diabetes, with poor diet, smoking, abstinence from alcohol, and low levels of physical activity also independently associated with increased diabetes risk[34].

The risk is higher for type 2 diabetes than type 1, which is relatively rare in the studied age groups [34]. On average, 20% of people with T2DM and 30% of those with type 1 diabetes mellitus (T1DM) are smokers, with smoking more prevalent among men and individuals from lower socioeconomic groups[78].

Several prospective studies have shown that smoking increases the risk of type 2 diabetes in both men and women[34]. Furthermore, the microvascular complications are more frequent among women than among men with diabetes[80]. Although men with diabetes consistently have a higher prevalence of smoking compared to women, smoking rates among women with diabetes have been rising, similar to trends in the general population[78]. A study by Thomas Ernst Doner et al. noted a significant increase in smoking prevalence among women in Austria over a seven-year period, particularly among those with chronic diseases, older age, lower education, and migration backgrounds [82]. Another study highlighted that smoking was widespread among young female T1DM patients and middle-aged T1DM and T2DM patients, warranting targeted smoking cessation campaigns. Smoking in these patients was linked to poor glycemic control and microalbuminuria, independent of other factors[83].

Research on patients with type 1 diabetes has reported negative effects of tobacco use on albuminuria and renal function, with smoking accelerating the progression of renal disease in those with type 2 diabetes[34]. The study by Nilsson PM et al. found that microalbuminuria is more common among smoking diabetics than nonsmokers and that smoking contributes to the risk factors associated with microalbuminuria and nephropathy in both T1DM and T2DM[83].

In diabetes care, smoking cessation is essential for improving glycemic control and reducing the risk of complications. The increased risk of diabetes decreases five years after quitting smoking and normalizes after 20 years[34]. A study by Wannamethee et al. found that cigarette smoking significantly increases diabetes risk, even after adjusting for age, BMI, and other potential confounders. The benefits of quitting smoking become apparent after five years,

with the risk reverting to that of never-smokers only after 20 years. Despite significant weight gain and a higher risk of diabetes in men who quit smoking within the first five years, the long-term benefits of smoking cessation outweigh the early adverse effects of weight gain[84].

Impact on quality of life

Despite a significant decline in tobacco use in many countries, smoking remains the leading health risk linked to early-stage disease and death. Several studies have explored the connection between smoking and health-related quality of life (HRQoL), showing that cigarette consumption is associated with lower QoL and mental well-being[85]. The link between smoking and mental health is not so clear. While most smokers express a desire to quit, many continue because they believe smoking offers mental health benefits. Both quantitative and qualitative studies show that regular smokers use cigarettes to cope with emotional issues, depression, anxiety, stabilize mood, relax, and relieve stress[86]. In fact smoking may worsen mental health through neuroadaptations from chronic use, causing nicotine withdrawal symptoms such as anxiety, depression, and irritability. In these cases, quitting smoking could improve mental health instead of worsening it[87].

The firm belief among some smokers that quitting will negatively impact their quality of life presents a major obstacle to cessation. Providing information about the long-term improvements in life satisfaction and quality of life after quitting could offer valuable insights for clinicians working with smokers concerned about the consequences of quitting. This knowledge could also be used to motivate and educate smokers on a larger scale, such as through media campaigns[88]. Cross-sectional studies have revealed that smokers tend to have lower HRQoL compared to non-smokers. Additionally, findings from several longitudinal studies suggest that individuals who smoked at baseline experienced worse physical HRQoL at follow-up than those who had never smoked. Furthermore, those who continued smoking from baseline to follow-up reported a decline in HRQoL at follow-up[89].

Smoking cessation interventions, like aerobic exercise, may also improve QoL. Exercise has immediate benefits for psychological well-being, such as reducing cravings and withdrawal symptoms. Additionally, regular exercise provides well-documented benefits for QoL, regardless of smoking status[90]. The impact of tobacco on smokers' HRQoL can vary based on factors like the number of cigarettes smoked and nicotine dependence. For example, heavy smokers tend to have lower HRQoL scores.

Dependent smokers report worse quality of life than non-dependent smokers. Other factors, such as age of smoking initiation, age of quitting, stages of change, and quit attempts, also play a role. Smokers who start before 15 have lower HRQoL, and quitting at an older age is linked to lower HRQoL scores. Smokers near quitting report worse physical health, while those not intending to quit show worse mental health. Additionally, smokers who unsuccessfully attempted to quit tend to have poorer HRQoL[91].

Tobacco smoking remains a leading cause of COPD, with passive smoking also contributing to respiratory symptoms and disease progression. Management of COPD focuses on clinical goals like preventing disease progression and minimizing symptoms, as well as improving health-related quality of life, including exercise tolerance and emotional well-being. Health status, functional status, and quality of life are often used interchangeably to describe this domain, with

HRQoL being crucial for assessing the impact of chronic diseases like COPD[92]. The HRQoL of COPD patients is influenced by multiple factors, including comorbidities like cardiovascular disease, diabetes, and osteoporosis, as well as risk factors such as smoking, low body weight, and inactivity. HRQoL measures the impact of disease on daily functioning.

Current COPD treatment protocols focus not only on symptom management but also on improving HRQoL. Improving quality of life involves reducing exacerbations, enhancing lung function, and encouraging smoking cessation, weight control, and physical activity[93].

As such, promoting smoking cessation among COPD patients is a critical priority for healthcare professionals. Given the chronic nature of COPD, home healthcare clinicians often have frequent interactions with patients, providing numerous opportunities to educate them about quitting smoking. It is essential for clinicians to feel confident in assessing patients' readiness to quit, as these discussions are crucial for encouraging cessation and improving QoL[94].

Conclusions

Smoking cessation remains the most effective intervention to slow disease progression and improve outcomes in COPD patients. This review highlights its significant benefits across multiple domains. By addressing the physiopathology of COPD, we have underscored how smoking cessation mitigates airway inflammation, reduces oxidative stress, and preserves lung function. Cessation leads to measurable improvements in respiratory symptoms, reducing dyspnea, cough, and exacerbation frequency.

Additionally, its positive impact extends beyond the respiratory system, lowering the risk of cardiovascular disease, diabetes, and lung cancer - common comorbidities in COPD patients.

Advances in imaging, particularly CT, have enhanced the early diagnosis of smoking-related complications, reinforcing the importance of quitting smoking to prevent further structural lung damage. Moreover, improved lung function following cessation translates into better exercise capacity, reduced hospitalizations, and overall improvements in daily activities. Patients report enhanced physical and mental well-being, with decreased anxiety and depression levels, highlighting the far-reaching impact of smoking cessation on quality of life. Given the overwhelming evidence, healthcare providers must prioritize smoking cessation strategies as a cornerstone of COPD management.

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Abbreviations

The following abbreviations are used in this manuscript:

Chronic obstructive pulmonary disease	COPD
World Health Organization	WHO
Forced expiratory volume in 1 s	FEV1
High-sensitivity C-reactive protein	hs-CRP
Neutrophil elastases	NE
Matrix metalloproteinase	MMP
Myeloperoxidase	MPO
Reactive oxygen species	ROS
Tumor necrosis factor-alfa	TNF-alfa
Transforming growth factor-beta 1	TGF-β1
Bronchoalveolar lavage	BAL
T-helper type 17	Th17
Membrane lipid peroxidation	LPO
Reactive nitrogen species	RNS
Forced vital capacity	FVC
Forced Expiratory Flow 25-75%	FEF 25-75
Carboxyhemoglobin	COHb
Six-Minute Walk Test	6MWT
Nicotine Replacement Therapy	NRT
High-Resolution Computed Tomography	HRCT
Lung cancer	LC
Cardiovascular disease	CVD
Coronary heart disease	CHD
Peripheral arterial disease	PAD
Abdominal aortic aneurysm	AAA
Myocardial infarction	MI
Coronary artery disease	CAD
Atherosclerotic cardiovascular disease	ASCVD
Systolic blood pressure	SBP
Diastolic blood pressure	DBP
Diabetes mellitus	DM
Low-density lipoprotein	LDL
High-density lipoprotein	HDL
Glycated hemoglobin	A1C
Type 2 diabetes mellitus	T2DM
Type 1 diabetes mellitus	T1DM
Health-related quality of life	HRQoL

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