Ministry of Higher Education

and Scientific Research

University of Diyala

College of Medicine

A Review Article in:

The effect of smoking on COVID-19 distribution

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

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2021 **2022**

بسم الله الرحمن الرحيم

(أَمَّنْ هُوَ قَانِتٌ آنَاءَ اللَّيْلِ سَاجِدًا وَقَائِمًا يَحْذَرُ الْآخِرَةَ وَيَرْجُو رَحْمَةَ رَبِّهِ ۗ
قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لَا يَعْلَمُونَ ۗ إِنَّمَا يَتَذَكَّرُ أُولُو الْأَلْبَابِ)

صدق الله العلي العظيم

من سورة الزمر الآية 9

Acknowledgment

All praise is to allah, my lord, god, you were always with me in my journey and I cant thank you enough for what you gave me. Thanks allah, all praise is to allah.

I owe a great many thanks to the great people who helped and supported me to complete this project.

My deepest thanks to (**Dr. Luma Taha**) my teacher and supervisor for guiding me in the article by correcting the mistakes and giving his valuable opinions in many aspect in both scientific facts and literature ones. I hope all the best and successes to her in her career and future**.**

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Summary

Smoking is the largest single risk factor for premature death in developed countries. Approximately one fifth of the deaths in the United States are attributable to smoking, and 28% of the smoking-attributable deaths involve lung cancer, 37% involve vascular disease, and 26% involve other respiratory diseases. More than 400 000 deaths per year and 30%. Other impacts at organs that aren't directly affected by smoke appear to follow a consistent pattern; women who smoke cigarettes tend to be estrogen-deficient in various ways. Smoking's antiestrogenic impact would, of course, exacerbate estrogen-deficiency issues like osteoporosis. In COVID-19, The novel emerging disease, has spread rapidly from Wuhan to other parts of China and to other countries. Smoking tobacco is also a known risk factor for severe disease and death from many respiratory infections. In the COVID-19 pandemic, questions have been asked about clinical outcomes for smokers, and whether they are equally susceptible to infection.

1.Introduction

Inhaling and exhaling gases from burning plant material is known as smoking. Smoking is done with a number of plant materials, such as marijuana and hashish, although it is most generally associated with tobacco, which is smoked in a cigarette, cigar, or pipe. Tobacco includes nicotine, an addictive chemical that has both energizing and sedative psychoactive effects. (1). According to the 2013–2014 National Adult Tobacco Survey (NATS), the United States' national prevalence for current tobacco product use was 21.3% in adults aged ≥18 years. Distribution of tobacco product use include: 17% for cigarettes, 1.8% for cigars/cigarillos/filtered little cigars, 0.3% for pipes, 0.6% for water pipes/hookah, 3.3% for electronic cigarettes, and 2.5% for smokeless

tobacco (2). These patterns contrast significantly with tobacco usage in the 1800s, when chewing tobacco and pipe tobacco were the most popular options due to the lack of mass-produced cigarettes. While still harmful, these less popular tobacco usage patterns were linked to less cancers and tobacco-related fatalities in theory (2).

Smoking is the largest single risk factor for premature death in developed countries. Approximately one fifth of the deaths in the United States are attributable to smoking, and 28% of the smoking-attributable deaths involve lung cancer, 37% involve vascular disease, and 26% involve other respiratory diseases. More than 400 000 deaths per year and 30% of all cancers in the United States are attributable to smoking. Lung cancer is the largest single cause of cancer-associated mortality and is the most common cause of smoking-related mortality in the United States. (3). Other impacts at organs that aren't directly affected by smoke appear to follow a consistent pattern; women who smoke cigarettes tend to be estrogen-deficient in various ways. Smoking's antiestrogenic impact would, of course, exacerbate estrogen-deficiency issues like osteoporosis (4).

In December 2019, a clustering pneumonia of unknown etiology occurred in Wuhan, Hubei Province, China. The emerging disease has spread rapidly from Wuhan to other parts of China and to other countries. Through a deep sequencing analysis, International Committee of Taxonomy of Viruses (ICTV) has designated the virus responsible for this epidemic pneumonia as SARS-CoV-2 (5). SARS-CoV-2 binds to ACE 2, (Angiotensin converting enzyme receptors type 2), the host target cell receptor. Active replication and release of the virus in the lung cells lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms. (6) The typical respiratory symptoms include

shortness of breath, fever, usually dry cough but may be productive, chest pain, sore throat, tiredness and anosmia. The non-respiratory symptoms include diarrhea, loss of appetite, loss of taste sense , neurological symptoms such as , headache , dizziness , altered mental status , Guillian-barre syndrome and rarely stroke (7).

Smoking tobacco is also a known risk factor for severe disease and death from many respiratory infections. In the COVID-19 pandemic, questions have been asked about clinical outcomes for smokers, and whether they are equally susceptible to infection, and if nicotine has any biological effect on the SAR-CoV-2 virus (the virus that causes COVID-19) (8).

Aim of article

To demonstrate the impact of smoking on the outcomes of COVID-19 infection.

2.Literature review

2.1. Prevalence of covid-19 among smokers

The risk factors for contracting symptomatic COVID-19 are not fully understood yet. Age and certain underlying health conditions are considered to be detrimental for disease outcomes. The World Health Organisation associated smoking with an adverse progression of the disease and called on smokers to quitting smoking. However, a review of 174 cohort studies revealed an unexpected low number of current smokers among subjects tested for SARS-CoV-2 infections.

The prevalence of current smokers suffering from symptomatic COVID-19 was frequently significantly lower than in the general population. Current smokers were at reduced risk of being tested positive

compared to former smokers and never smokers, which might have been caused by different testing frequencies, but were at higher risk for severe symptomatic COVID-19 (9). This low prevalence of current smokers among COVID-19 patients led to the hypothesis that smoking/ nicotine uptake might have a preventive effect (10).

A systematic review assessing prevalence of current smokers who were hospitalized for COVID-19 reported a pooled prevalence of 6.5% and propose that in view of the lower than expected prevalence of current smokers compared to population estimates, current smoking is not a predisposing factor for hospitalization and smoking and/or nicotine may exert a protective effect against severe COVID-19 (11).

2.2 COVID-19 and gender:

During the current COVID-19 pandemic is an interesting and highly significant observation reported that much more common spread and mortality rate of this coronavirus in men as compared to in women. Allowing to an analysis of roughly 45,000 reported cases in China, the mortality rate was 2.8 and 1.7% in men and women, respectively (12).

2.3 Age effect on COVID-19 patients

Increased age appears to be a strong risk factor for COVID-19 severe outcomes. However, studies do not sufficiently consider the age-dependency of other important factors influencing the course of disease. A meta-analysis showed that The crude effect of age (5.2% and 13.4% higher risk of disease severity and death per age year, respectively) substantially decreased when adjusting for important age-dependent risk factors (diabetes, hypertension, coronary heart disease/cerebrovascular disease, compromised immunity, previous respiratory disease, renal disease). Adjusting for all six comorbidities indicates a 2.7% risk increase for

disease severity, and no additional risk of death per year of age. The indication of a rather weak influence of age on COVID-19 disease severity after adjustment for important age-dependent risk factors should be taken in consideration when implementing age-related preventative measures (13).

2.4 Smokers vs. non-smokers

Smokers compared with nonsmokers in several transcriptomic data sets of lung samples from healthy never- and ever smokers and patients with chronic obstructive pulmonary disease. Also, they report an increase in ACE2-producing goblet cells in ever-smoker versus never-smoker lungs. These findings have putatively important implications for patients with COVID-19 because ACE2 has been shown to be the receptor used by SARS-CoV-2 to enter the host cells and yet seem in contrast with the consolidated epidemiological data worldwide indicating a low prevalence of active smokers among patients with COVID-19 (14).

Spatial analysis involving 175 countries showed that the percentage of the total smoking population was inversely associated with COVID-19 at the global level. In Mexico, among 89756 laboratory-confirmed positive cases (retrospective case series used a publicly available nation-level dataset released on May 31, 2020, by the Mexican Ministry of Health), current smokers were 23% less likely to be diagnosed with COVID-19 compared to non-smokers. However, having COPD (among other comorbidities) was associated with hospitalization and adverse outcomes.

Current smoking was not linked to unfavorable outcomes. Similarly, an ecological study found a statistically significant negative association between smoking prevalence and the prevalence of COVID-19 across the 38 European nations, after controlling for confounding factors. However,

it could not demonstrate a direct association between smoking prevalence and COVID-19 mortality (15). A preliminary study that analyzed the data available in published articles showed a lower prevalence of smoking in COVID-19 patients compared to the regional average (16).

2.5 Physiological changes in smokers

Cigarette smoke induces epigenetic modifications of the bronchial epithelium, leading to mucous (goblet) cell metaplasia. As goblet cells are a major source of ACE2 in the lung, this could, in part, justify the increased levels of ACE2 found by Cai et., al, in lungs of smokers. However, goblet cells are also the main source of mucous, which provides an essential first host barrier to inhaled pathogens that can prevent pathogen invasion and subsequent infection (17). Robust evidence suggests that several mechanisms might increase the risk of respiratory tract infections in smokers. Smoking impairs the immune system and almost doubles the risk of tuberculosis infection (latent and active) due to impairment of immune function; specifically, smoking affects the macrophage and cytokine response and hence the ability to contain infection. Similarly the risk for pneumococcal, legionella, and mycoplasma pneumonia infection is about 3–5-times higher in smokers. Users of tobacco and e-cigarettes have increased adherence of pneumococci and colonization, as a result of the up regulation of the pneumococcal receptor molecule (platelet activating receptor factor); smokers are also 5-times more likely to contract influenza than nonsmokers (18).

2.6 Impact of covid-19 on smokers

Recently, *Patanavanich et al*. conducted a systematic review and meta-analysis to explore the association of smoking with coronavirus (COVID-19) progression, based on 18 retrospective studies and 1 case

series report. They found that smoking was a risk factor for COVID-19 progression. After reading this article, we found three questions that should be considered (19).

The role of cigarette smoking/nicotine (or whatever else is contained within cigarette smoke) in the scientific discussion on COVID-19 ignores the fact that smoke cessation has to be discouraged to avoid COVID-19 pulmonary complications (this seems obvious for scientists and physicians) but references the scientific importance of the strong epidemiological data coming from all the countries that hospitalized patients with SARS-CoV-2 related pneumonia show quite low percentages of active smokers (20).

Nevertheless, accumulating biological and clinical evidence suggests also that the relationship between active smoking and COVID-19 is not straightforward or unidirectional, and contributes to portray this intricate link as a double-edged sword, so that drawing definitive conclusions may be premature and even misleading. On the one hand, whether cigarette smoking-induced up-regulation of the natural SARS-CoV-2 receptor ACE2 in human cells would increase the likelihood of being infected must be considered. However, to the contrary, increased expression of this enzyme may considerably attenuate the risk of developing the devastating lung and systemic injuries characterizing severe and critical forms of COVID-19. ACE2 plays a pivotal role in the pathogenesis of pulmonary disease and its evolution towards respiratory distress, whereby this enzyme catalyzes the conversion of angiotensin II (AngII) into angiotensin 1-7 (Ang1-7), a degradation peptide which strongly counteracts the unfavorable pro-inflammatory, vasoconstrictive, oxidative and fibrotic activity of the parental hormone AngII (21).

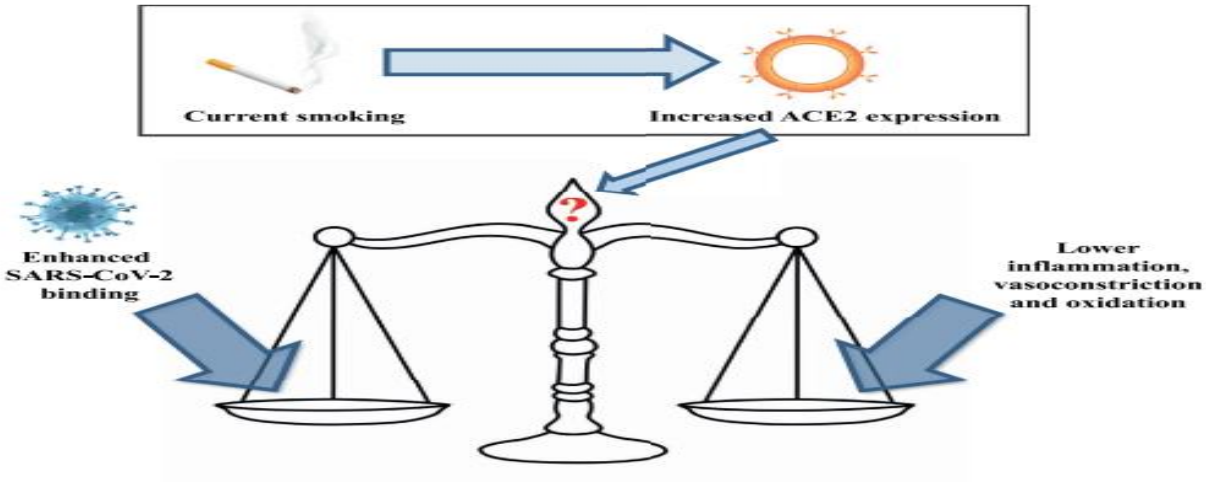

Figure 1. The intricate and still enigmatic relationship between current smoking and coronavirus disease (COVID-19).

A meta-analysis found that current smokers have an increased risk of presenting to hospital with severe COVID-19 and are approximately twice as likely to experience severe or critical COVID-19 as former or never-smokers (22).

According to a cohort study, Among 9,991 consecutive patients diagnosed with COVID-19, 2,212 (22.1%) patients were self-reported smokers (406 current and 1806 former). Current smoking was not associated with an increased risk of hospitalization, in-hospital mortality, ICU admission, or intubation. Similarly, former smoking was not associated with an increased risk of hospitalization, in-hospital mortality, ICU admission, or intubation. Furthermore, smoking (current or former) was not associated with an increased risk of hospitalization, in-hospital mortality, ICU admission or intubation (23).

Nicotine is known to have an effect on the renin-angiotensin system (RAS) by up-regulating the receptor axis, ACE/angiotensin (ANG)-II/ANG II type 1 and down-regulating the ACE-2/ANG-(1–7)/Mas receptor axis, which may in turn contribute to cardio-pulmonary pathologies. In a recent editorial, it has been proposed that the nicotinic

cholinergic system could be implicated in COVID-19 infection because COVID-19 clinical manifestations such as a cytokine storm, may be explained by the cholinergic anti-inflammatory dysfunction. Alpha7 nicotinic acetylcholine receptor (α7-nAChR) can potentially modulate pro-inflammatory cytokine secretion, suppressing a cytokine storm. The possible mechanism may be that nicotine exposure upregulated the expression of ACE-2, and induced phospho-S6 ribosomal protein (Ser235/236), Akt1, phospho-Akt (Ser473), phospho-Akt (Thr308), and phospho-p44/42 MAPK (Thr202/Tyr204) in vitro; subsequent gene silencing of α7-nAChR appeared to significantly dampen this response (24).

Meta-analyses, however, have suggested that active smoking might be associated with a worse prognosis of COVID-19. This might be related to chronic lung and vascular injury induced by smoking, in a disease characterized by a marked pro-thrombotic state and pro-inflammatory state. Accordingly, it is possible that smoking may confer some protective factors against development of SARS-CoV-2 infection, but might be associated with worse disease once acquired. However, smoking is also a risk factor for social isolation. Therefore, it is possible that people who smoke are simply less exposed to potential infected contacts (25).

3. Conclusion

There is contradictions in literature regarding the impact of smoking impacts and effect on the prognosis of COVID-19 and there is progressing idea of the concept of double edged sword about the smoking. Further investigations and researches is needed.

4.Recommendations

We recommend that the smokers should undergo special smoking-quit programs whether there is an association or not. Even if there is a chance that the smoking may decrease the burden of infection, it will destroy the lungs and alveoli in the future so quitting is much recommended.

We recommend the health authorities to increase their efforts in their publicity campaigns to encourage people to quit smoking in order to decrease the burden of respiratory diseases and ecosystem pollution.

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