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Letter to Editor

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Are Patients With Alcohol Use Disorders at Increased Risk for Covid-19 Infection?

Gianni Testino*

Unit of Addiction and Hepatology, Alcohological Regional Centre, ASL3 c/o Polyclinic San Martino Hospital, Padiglione 10, Piazzale R Benzi 10, 16132 Genova, Italy

*Corresponding author: Unit of Addiction and Hepatology, Alcohological Regional Centre; ASL3 c/o Polyclinic San Martino Hospital, Padiglione 10, Piazzale R Benzi 10, 16132 Genova, Italy. Tel./Fax: 0039-010-5552769; E-mail: gianni.testino@hsanmartino.it; gianni.testino@asl3.liguria.it

The receptor sites of Covid-19 (via angiotensin-converting enzyme 2—ACE2) are present in the pulmonary, intestinal, renal and hepatic sites (in particular in correspondence of cholangiocytes). Other locations are being identified.

Covid-19 (2019-nCoronavirus [CoV]) is a new CoV with similarity to severe acute respiratory syndrome coronavirus (SARS-CoV). Chen *et al.* (2020) recently performed a structural analysis of the receptor binding domain (RBD) of spike glycoprotein responsible for the entry of CoV into host cells. The Covid-19 RBDs have amino acid sequences that are 72% shared with SARS-CoV. Covid-19, however, has a distinct loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV. This variation allows it a stronger interaction with ACE2. This results in easier penetration and diffusion, especially in the lower respiratory tract (ACE2 is expressed in large quantities in alveolar type 2 cells).

It is known that 'fragile' patients are predisposed to contracting this virus and to develop serious complications, such as atypical pneumonia and acute respiratory distress syndrome (ARDS).

The patient with alcohol use disorder (AUD) is 'fragile'. In this review we show that he is at greater risk of contracting both viral and bacterial infections.

Covid-19 infection and AUD are both relatively common disorders. Worldwide, ~2.4 billion people consume alcohol, with 1.5 billion (1.4–1.6) current male drinkers and 0.9 billion (0.8–1.0) current female drinkers. In the western world, per capita consumption varies from 8 to 12 L, in Asia there is a progressive increase (for example in China 6–8 L) (Manthey *et al.* 2020). The past year prevalence of AUD ranges from 8.8% (Europe) to 0.8% (Eastern Mediterranean Region) of the adult population (WHO 2018).

Moreover, the media report an increase in alcohol consumption during this pandemic due to social estrangement, self-isolation resulting in a sense of loneliness and possible depressive state.

It is well known that there is a dose dependent correlation between viral infections and alcohol consumption (Testino *et al.*, 2016; Ruuskanen *et al.*, 2011).

Hepatitis C virus (HCV) and/or Human immunodeficiency virus (HIV) are present in 30–40% of patients with AUD and 70% of HCV and/or HIV patients have a history of AUD (Testino *et al.*, 2016). Heavy drinkers are at an increased risk of a worsened course of HIV/acquired immune deficiency syndrome (Eghe *et al.*, 2019).

It is also known that alcohol consumption increases the risk of acquired community infections (Simou *et al.*, 2018).

Pulmonary infectious disease risk is present for both moderate and risky-harmful consumption.

No differences were found between hazardous and moderate drinking according to the Alcohol Use Disorders test-C (AUDIT-C) in lung function, which was worst in heavy drinkers and those with high carbohydrate-deficient transferrin (a marker of heavy drinking), compared to non-drinkers (Frantz *et al.*, 2014). This risk is independent of tobacco smoking.

Chronic alcohol consumption (CAC) affects all components of immunity (Happel and Nelson, 2005). Experimental studies have suggested that CAC increases the risk of severe influenza virus infections by strengthening the inflammatory reaction and stimulating the CD8 response (Szabo and Saha, 2015; Meyerholz *et al.*, 2008).

Ethanol is able to interact forcefully at different levels, acting both on natural or innate immunity (phagocytosis, natural killer cells—NK, complement) and on specific or acquired immunity (Szabo and Saha, 2015; Meyerholz *et al.*, 2008).

In particular, the activity of NK cells is altered by the following actions of ethanol: interference of the bond between NK and target cell, modification of the production and use of some cytokines, alteration of cytolytic activity, alteration of signal transduction and direct effect on the neuro-endocrine system (Pasata *et al.*, 2015).

Experiences in both animals and humans have shown a reduction in the number of peripheral T cells, alteration of the balance between the various T components, inhibition of the activation of T cells, reduction in the functioning of these cells and finally an increase in apoptotic mechanisms. To all this is added a reduction of peripheral B cells with a simultaneous alteration of the production of immunoglobulins (Pasata *et al.* 2015; Bartoletti *et al.*, 2016).

Szabo and Saha (2015) affirm that the proinflammatory effects (interleukin-1, tumor necrosis factor alpha, interleukin-6) of CAC play a major role in the pathogenesis of lung disease. In addition to

promoting proinflammatory immune responses, alcohol also impairs the production of anti-inflammatory cytokines.

Other alcohol induced mechanisms are the following: reduction of the pharyngeal tone, increased risk of aspiration of micro-organisms, worsening of alveolar macrophage function and malnutrition.

A particularly fragile patient is one suffering from alcohol related liver disease (ALD).

In this subject, there is an increased risk of infections (bacterial, viral and fungal) especially in the urinary and respiratory levels (Testino *et al*., 2020).

Respiratory infections often involve both viral and bacterial organisms. Some viral infections (e.g. influenza viruses or parainfluenza viruses) favor bacterial overlap and growth (e.g. Klebsiella and Streptococcal Pneumoniae). During ALD one of the mechanisms of viral action (strengthened by the action of ethanol) favoring bacterial overlap is the overexpression in the lung of some adhesion proteins (hemagglutinin, neuraminidase) and the alteration of cell junctions (Bosch *et al*., 2013).

In animal models of pulmonary infections, alcohol administration is associated with adverse clinical parameters and increased lung damage (Szabo and Saha, 2015).

Furthermore, alcohol and Covid-19 alter the microbiota and damage intestinal cell junctions. This results in translocation of lipopolysaccharides (LPS) and pathogen-associated molecular patterns (PAMPs) from the gut. LPS and PAMPs are specifically recognized by receptors called pattern-recognition receptor (PRRs) located at the surface or within innate immune cells, e.g. macrophages and hepatic Kupffer cells. The engagement of PRRs (among PRRs there are toll-like receptors) results in the production of proinflammatory cytokines (Sarin *et al*., 2019).

The inflammatory chaos that is created facilitates the onset of respiratory failure and multi organ failure.

Moreover, it is well known that CAC independently increases the incidence of ARDS in critically ill patients at risk for the syndrome. The relative risk of developing ARDS attributed to alcohol intake was 3.7 (95% CI, 1.83–7.71) (Crews *et al*., 2006) Alcohol causes severe oxidative stress and depletion of the critical antioxidant glutathione in the alveolar space and susceptibility to sepsis-mediated acute lung injury (Moss *et al*., 2000).

Bechara *et al*. (2003) affirm that chronic ethanol intake increases angiotensin II type 1 receptor (AT2) expression in the alveolar epithelium and enhances tumor necrosis factor-alpha and angiotensin II-induced cytotoxicity, both of which act via AT2. These findings reveal that selective AT2 receptor inhibition could limit the development of acute lung injury in patients affected by AUDs.

In conclusion alcohol consumption, significantly increases the risk of contracting bacterial and viral lung infections (including Covid-19).

This conclusion is supported by the well-known fact that there is a correlation between alcohol consumption (also social-moderate) and the amount of ACE2 present in the body and in particular in the respiratory site. Okuno *et al*. (1986) evaluated serum ACE activity in 47 ALD hospitalized patients. Compared to the controls, the ACE activity at the inlet was found to be significantly high (42.5 ± 16.6 U/ml vs. 32.4 ± 9.6 U/ml; $P < 0.005$). An increase in ACE levels above the normal value of 42 U/ml (mean ± SD) was found in ∼36%. This increase is also present after 4 weeks of alcohol abstention.

It is appropriate to inform the population that the consumption of alcoholic beverages (especially risky/harmful consumption) correlates with a greater probability of viral lung infection.

Therefore, in a historical period characterized by a Covid-19 pandemic, doctors and all health professionals must motivate citizens not to consume alcohol or limit consumption to no more than one alcoholic unit/day (low risk consumption) (Scafato *et al*., 2020). This is especially true in the elderly population with polypathology (diabetes mellitus, heart disease, liver disease, etc.) and polytherapy.

While waiting to develop appropriate antiviral therapies and vaccines, the scientific community must stimulate scientific research on the relationship between alcohol intake (one of the most consumed drinks in the world) and Covid-19 infection.

CONFLICT OF INTEREST STATEMENT

None declared.

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