Is There a Role for Environmental and Metabolic Factors Predisposing to Severe COVID-19?

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ABSTRACT

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic affects people around the world. However, there have been striking differences in the number of infected individuals and deaths in different countries. Particularly, within Central Europe in countries that are similar in ethnicity, age, and medical standards and have performed similar steps of containment, such differences in mortality rates remain inexplicable. We suggest to consider and explore environmental factors to explain these intriguing variations. Countries like Northern Italy, France, Spain, and UK have suffered from 5 times more deaths from the corona virus infection than neighboring countries like Germany, Switzerland, Austria, and Denmark related to the size of their respective populations. There is a striking correlation between the level of environmental pollutants including pesticides, dioxins, and air pollution such as NO_2 known to affect immune function and healthy metabolism with the rate of mortality in COVID-19 pandemic in these European countries. There is also a correlation with the use of chlorination of drinking water in these regions. In addition to the improvement of environmental protective programs, there are possibilities to lower the blood levels of these pollutants by therapeutic apheresis. Furthermore, therapeutic apheresis might be an effective method to improve metabolic inflammation, altered vascular perfusion, and neurodegeneration observed as long-term complications of COVID-19 disease.

Introduction

The 2020 pandemic of SARS-CoV-2 infection did not respect any borders and did not spare any regions of the world. Nevertheless, there are striking differences in the mortality rates and the occurrence of severe courses of the disease in different countries [1, 2]. This had been attributed to obvious differences of dissemination and efficiency of containment in different countries. It had also been related to the lack of knowledge of truly SARS-CoV-2 positive individuals versus the number of ill patients. Obviously, the availability and capacity to test for the virus are completely inconsistent between and sometimes even within different countries.

Finally, the different age profile, occurrence of comorbidities, quality of health care systems and even genetic predispositions have been blamed for the striking variations in the incidence of critical disease and lethal outcome [3–8].

Even if all these factors will play an important role they do not fully explain the reality of what we are seeing now.

Why did so many more casualties occur in Italy, France, Spain, the UK, and the United States than in other European countries like Germany, Austria, Switzerland or Scandinavia?

Even if methods of containment and exposure as well as infection rates play a crucial role, such drastic discrepancies remain currently inexplicable.

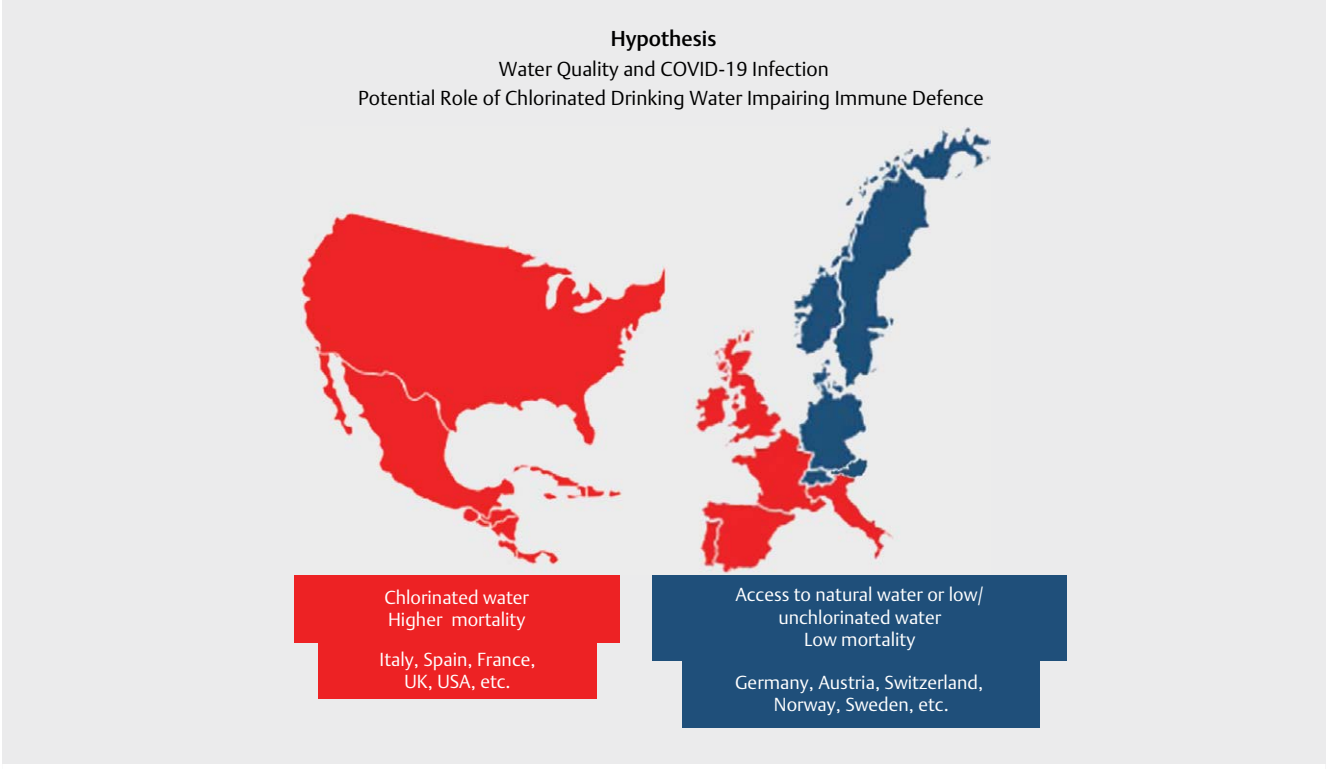
All these countries do have modern and efficient health care systems with more or less similar shortcomings. In all these countries, there are similar elderly populations with no major demographic differences. The same is true for the rate and distribution of comorbidities that had been defined as risk factors for severe COVID-19 disease such as diabetes, hypertension or heart disease [8–11]. There is currently no clear evidence for major differences in genetic predisposition between the populations of these Western countries.

Is There any Other Plausible Explanation?

Here we would like to open the discussion with a provocative hypothesis regarding these enigmatic differences in incidence of severe COVID-19 disease. We suggest that the use of chlorinated drinking water and/or other environmental pollutants could play a key role in the variation of susceptibility to the contraction of severe corona virus infection in these Western countries. Across Africa, South America, and Asia, tap water is unsuitable for drinking due to contamination and general hygienic conditions, which differ strongly from the Western world.

In contrast, in all countries of the Western world water can be used for drinking from the tap. However, there is one crucial difference. Whereas in countries like the US, UK, France, Spain, and Italy tap water is highly chlorinated, countries like Germany, Austria, Switzerland, and Scandinavia refrain from chlorination of their drinking water. In fact, we found an intriguing correlation of the rate of chlorination of tap water in different countries with the incidence of severity of COVID-19 disease (▶ **Fig. 1**).

Those countries that have not been exposing their populations to high levels of chlorinated water in the last decade exhibit a 2-20 fold lower death rate in the current pandemic. This is a most striking observation, which may be a mere coincidence but it should be worthwhile to seriously consider this conundrum.



▶ **Fig. 1** Distribution of water quality and COVID-19 infection.

Effects of Chlorinated Water on our Immune System

There is indeed ample and substantial evidence that chlorinated water may affect various functions of our immune system.

Chlorine gas is a formidable lung toxin [12]. Airway injury occurs due to oxidative damage, swarming of inflammatory cells, and resultant airway hyper-responsiveness [13]. Lipid peroxidation is a major damage event in the lung, and may critically affect the airway surface layer and its surfactant capacity [14, 15]. There is limited data regarding the availability of ingested or transdermally absorbed chlorine to partake in such processes.

When water is disinfected with chlorine and ingested, chlorinated, and brominated, mixed bromochloro acetates are formed [16]. Earlier studies in mice and rats exploring the potential of immunotoxicity of bromochloromethane and other disinfection by-products (DBPs) did not reveal any major effects on cellular or humoral immunity [17, 18]. Other research using experimental animals, however, reported a suppressive effect of chlorine-based drinking water on macrophage function [19, 20]. The intracellular redox status experiences depletion of reduced glutathione (GSH) [12]. The haloacetates, trichloroacetate, dichloroacetate, and their brominated analogues induce hepatic lipid peroxidation [16], and the liver is usually considered to be the target for lipid peroxidation processes related to chlorinated water [21]. The release of lipid toxins may be enhanced by SARS-CoV-2 driven liver disease [22], which is more prevalent in more severe systemic COVID-19 disease [23].

However, the small amounts of chlorine used for water disinfection, or evaporating from swimming pool surfaces may result in an attack of phospholipids by chlorine species, inducing chlorinated phospholipids. This consideration brings lipid peroxidation products into the center of attention [24]. Sodium chlorate ($NaClO_3$) is a by-product during disinfection of drinking water with chlorine dioxide. Human erythrocytes exhibit a significant increase in protein and lipid peroxidation, and a concomitant decrease in reduced glutathione [25, 26]. They offer an attractive shuttle system of peroxidated lipids, which come in indirect contact with the alveolar surface, as it is separated from the bloodstream by a membrane as thin as 0.2 µM. Chlorine driven ROS-induced lipid transformations without oxygen lead to formation 2-hexadecenal from sphingolipids. 2-Hexadecenal has a potent adverse biological potential. 2-Chloro-, and 2-bromo-substituted fatty aldehydes are produced by hypochlorous acid-induced endothelial damage, supposing a perfect storm at the lung-blood endothelial interface [27]. Whilst the exact pathways are still unknown it is plausible how ingested chlorine could via systemically released hepatic lipid peroxidation products, and by-products of lipid peroxidation in erythrocyte walls, be shuttled to the critical site of SARS-CoV-2 mediated disease: the alveolar ductal system and its neighboring endothelial surface [28–30].

More recent work has elucidated the role of polychloroaminated biphenyls on alterations of the innate immune response of marine mammals [31]. Interestingly, even swimming in a pool with chlorinated water induces an acute change of serum immune markers in humans [32]. Thus, in both males and females there was a significant decrease in cytokines following 40 min swimming in a chlorinated pool [32]. Likewise in the blood of children with a high content of organochlorine compounds in drinking water an imbalance of cellular components of innate and adaptive immunity was found [33]. This suggests both acute and chronic effects of chlorinated water on the human innate immune response may interfere with the capacity of an individual to fight a virus infection.

Finally, chlorinated water may alter microbiome composition, the immune-gut barrier, and gene expression of intestinal cells [33]. Thus, numerous typical chlorinated disinfection by-products altered specifically genes in intestinal cells associated with immune and inflammation pathway. Therefore, these environmental aspects of the coronavirus pandemic need to be explored to develop better strategies and protection of our populations for the future.

Other Environmental Pollutants Impairing Immune Function

Beyond the role of chlorination in drinking water there may be other environmental pollutants playing a key role in causing a predisposition for viral infections such as by SARS-CoV-2. One of the most devastating chemical accidents occurred in 1976 in Northern Italy in Seveso, which also was an epicenter of the COVID-19 pandemic. The exposure of the population to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induced major medical problems including effects on the hormonal, metabolic, and immune systems. TCDD triggers a wide range of immunotoxic effects on both the humoral, cellular and also the innate immune response and interacts with the aryl hydrocarbon receptor [34–39]. It alters type 3 innate lymphoid cells in the colon and the entire intestinal tract [40, 41]. These effects on the immune system may even have been transferred to the next generation [42, 43]. Thus, offspring of pregnant rats exposed to TCDD exhibited an immunosuppression characterized by reduced thymus weight, reduced virus-associated natural killer (NK) cell, and specific antibody responses [42].

Furthermore, it has been shown that suppression of immune function led to an enhanced susceptibility to viral infections including influenza [44, 45]. In fact, even low levels of TCDD exposure lead to enhanced mortality to the influenza virus [45]. In addition to TCDD, exposure to pesticides may play an important role. Particularly, in Northern Italy more than 65 percent water samples from rivers and lakes exhibit high levels of pesticides including *p*,*p*′-DDE or *p*,*p*′-DDT and glyphosates.

These pesticides have been shown to exert a significant effect on the immune system. Persistent organic pollutants including 16 polychlorinated biphenyls and organochlorine factors increased pro-inflammatory cytokines, activated macrophages, and enhanced immunosenescence [46–48].

In experimental settings, glyphosate exposure may cause toxic effects on intestinal morphology, antioxidant capacity and barrier function [49].

PFAS, per- and polyfluorinated alkyl substances, are a huge class of non-classical persistent organic pollutants (POPs), which have been produced since the 1940s. Common use of these compounds, for example as surfactants, stain repellents, fire containment and many more applications has caused widespread environmental contamination. Human exposure occurs amongst other exposure pathways through air, water and particularly through terrestrial and aquatic food chains, including through food processing and packaging processes. Perfluorooctanesulfonic acid (PFOS) and perfluo-

rooctanoic acid (PFOA) represent the two most frequently studied members of this large family of molecules. Although no geographical differences in the exposure to these chemicals can be deduced, they have to be discussed in the light of the COVID-19 pandemic.

In 2018, the European Food Safety Authority (EFSA) performed a risk assessment on PFOS and PFOA on human health. Although the risk assessment was primarily based on associations of the compounds to serum cholesterol levels, antibody response to vaccination in children was also identified as a critical effect [50]. This risk assessment is currently updated and the opinion is out for public consultation. In essence, it is confirmed for humans and animals, that levels of PFOS and PFOA are inversely linked to functionality of the immune system. The most significant concern regards the strong inverse association of PFAS blood levels and antibody response for example, following booster vaccinations to diphtheria and tetanus, particularly in children as shown on the Faroe Islands [51] and in Germany [52]. Supporting information from animal studies is available [53]. Perhaps more relevant to COVID-19 is a less pronounced inverse association with antibody titers [54].

Finally, important data link nitrogen dioxide (NO_2) levels to COVID-19 fatality rates [55]. Spatial analysis has been performed on a regional scale and combined with the number of death cases taken from 66 administrative regions in Italy, Spain, France, and Germany. Results show that out of the 4443 fatality cases, 3487 (78 %) were in five regions located in Northern Italy and central Spain. Interestingly, the same five regions exhibited the highest NO_2 concentrations combined with downwards airflow which prevents an efficient dispersion of air pollution. These results suggest that the long-term exposure to this pollutant may be an important contributor to fatality caused by the SARS-CoV-2 virus in these regions [55].

An explanation for susceptibility to progress to severe Covid disease may be provided by the observation that high levels of NO_2 affect innate immunity in the lung [56] and induce airway inflammation [57].

In summary, there is evidence that environmentally persistent compounds, particularly perfluorinated compounds and nitrogen dioxide, may compromise the immune response. Whilst no particular geographical association can be determined for perfluorinated compounds, regional segregation of death rates with NO_2 levels may provide more direct clues.

Effect of Environmental Pollutants on Lipid Levels and Cardiometabolism

All these environmental pollutants including dioxin-related chemicals as well as pesticides induce significant hormonal and metabolic alterations. Thus, exposure to DDT increases the incidence of diabetes in the NOD mouse model [58].

Acute dioxin exposure led to long-term metabolic consequences in mice [59]. Organochlorine pesticides may potentially mediate insulin resistance [60]. Population-based studies demonstrated an association between polychlorinated dibenzo-*p*-dioxin and polychlorinated biphenyls and the incidence of diabetes and hyperlipidemia [61]. Given the fact that diabetes, obesity and the metabolic syndrome are major risk factors for severe COVID-19 infections, the role of these environmental factors is even more prominent. Of course, the risk of microbial contamination has to be balanced with the potential risk of disinfection by-products [62].

Environmental pollution has been correlated with severe dyslipidemia predisposing for metabolic syndrome and cardiovascular disease [63–65]. Organochlorine pesticides significantly aggravated disorders of fatty acid metabolism [66].

Similarly workers exposed to dioxin reportedly had elevated lipid levels [67]. Hyperlipidemia contributed to the higher role of atherosclerotic plaques and ischemic heart disease in these individuals [68].

Role of Lipids, Environmental Pollutants, and Therapeutic Apheresis

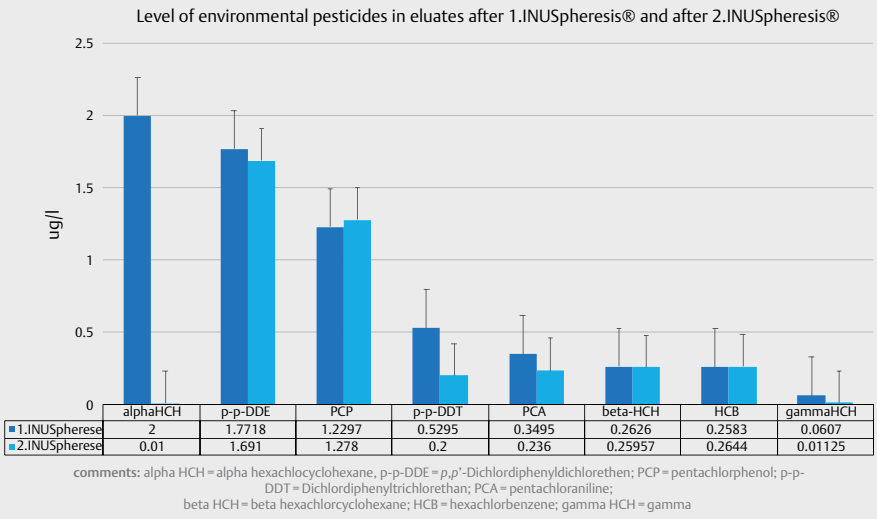
Changes in the lipid metabolism have been described in survivors of SARS-CoV infections [69]. Recovered SARS patients had increased phosphatidylinositol and lysophosphatidylinositol levels after 12 years, which might be also a result of treatment with high doses of methylprednisolone. Therefore, long-term effects of therapeutic interventions on the lipid metabolism should be considered in COVID-19 patients.

The impact of the lipoprotein metabolism on the clinical outcome in COVID-19 patients is currently not well understood. Recently, the impact of underlying cardiovascular disease (CVD) and myocardial injury on fatal outcomes in patients with COVID-19 has been described [70–72]. This study compared 52 patients with and 135 patients without elevation of troponin T (TnT) levels. Total, high-density lipoprotein, and low-density lipoprotein (LDL) cholesterol levels did not differ between both groups, but patients with elevated TnT levels had higher triglyceride levels. The inflammatory biomarkers high-sensitivity C-reactive protein and procalcitonin were significantly increased in patients with elevated TnT levels.

Other strategies to lower lipoprotein levels might represent interesting novel therapeutic approaches. In general, lowering LDL cholesterol and lipoprotein(a) levels could have beneficial effects like upregulation of ACE2 and prevention of cardiovascular complications during COVID-19 infection. Lipoprotein apheresis could be an attractive alternative therapeutic approach to treat critically ill patients. Apheresis has been shown to mediate lipid-lowering and anti-inflammatory effects [73]. This might mediate beneficial effects in COVID-19 patients with elevated CRP levels and inflammation.

Therefore, lipoprotein apheresis using rigidly implemented isolation measures might be a novel protective strategy in the treatment of COVID-19 patients. The European Group – International Society for Apheresis e.V. (E-ISFA) – has recently joined the German Center for Infection Research, the ESCMID Emerging Infections Task Force and a number of other institutions including the Robert Koch Institute in the LEOSS (Lean European Open Survey on SRAS-CoV-s Infected Patients) registry. This is an open, international and anonymous registry covering all aspects of COVID-19 infections from diagnosis, laboratory measurements over medical treatments to clinical outcomes (https://leoss.net). This initiative will help defining the impact of apheresis therapy on COVID-19 patients.

Furthermore, therapeutic apheresis is an efficient biophysical method to remove metabolic inflammatory immunological and environmental components from the blood of patients. Many patients with severe COVID-19 infection exhibit lymphopaenia which



▶ **Fig. 2** Level of environmental pesticides before and after therapeutic apheresis (INUSpherese®).

may lead to secretion of high amounts of inflammatory cytokines and cytokine storm [74–76].

Specifically therapeutic environmental apheresis (INUSpherese®) may be useful. We have previously shown that this method allows an effective removal of lipoproteins, inflammatory cytokines as well as environmental pollutants. This includes a reduction of heavy metals, but also a reduction of environmental pesticides (▶ **Fig. 2**). Environmental apheresis® is therefore useful to improve parameters of metabolic inflammation and hyperlipidemia, which have been shown to be major risk factors for the development of severe Coronavirus disease 2019. Furthermore, it has been shown to improve neuroinflammation and polyneuropathy [73, 77]. Thus, the removal and reduction of environmental pollutants together with the reduction of lipids and inflammatory factors may provide a protective mechanism for prevention and mitigation of severe corona virus infections.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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