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PROBLEMS & PARADIGMS

Prospects & Overviews

Does chronic inflammation cause acute inflammation to spiral into hyper-inflammation in a manner modulated by diet and the gut microbiome, in severe Covid-19?

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Abstract

We propose that hyper-inflammation (HYPi) is a ''runaway'' consequence of acute inflammation (ACUi) that arises more easily (and also abates less easily) in those who host a pre-existing chronic inflammation (CHRi), because (i) most factors involved in generating an ACUi to limit viral proliferation are already present when there is an underlying CHRi, and also because (ii) anti-inflammatory (AI) mechanisms for the abatement of ACUi (following containment of viral proliferation) are suppressed and desensitized where there is an underlying CHRi, with this causing the ACUi to spiral into a HYPi. Stress, pollution, diet, and gut microbiomes (alterable in weeks through dietary changes) have an intimate and bidirectional cause-effect relationship with CHRi. We propose that avoidance of CHRi-promoting foods and adoption of CHRi-suppressing foods could reduce susceptibility to HYPi, in Covid-19 and in other viral diseases, such as influenza, which are characterized by episodic and unpredictable HYPi.

KEYWORDS
Acute inflammation, Chronic inflammation, Covid-19, Cytokine storm, Diet, Gut inflammation, Gut microbiome, Hyperinflammation, Systemic inflammation

Exposure to viruses is a fait accompli for much of the planet's population. With SARS-CoV-2, successive waves of infection by new mutants and variants suggest that everyone is at risk of being exposed to a greater or lesser degree, either sooner or later. It is important to identify those with the highest probability of developing severe disease, in order to focus efforts at mitigation or prevention. This article discusses factors that might predispose individuals to developing severe Covid-19. It argues that more attention must be paid to the possibility of diet-derived chronic inflammation (CHRi) being the most important, and fundamental, of all predisposing factors.

COVID-19: DESCRIPTORS AND FACTORS AFFECTING SUSCEPTIBILITY TO SEVERE DISEASE

Early descriptors

Early Covid-19 reports indicated the following: (a) pneumonia is the most serious consequence of the disease;[1] (b) infection involves only respiratory epithelial cells rich in ACE2 membrane receptors;[2] (c) infection causes severe symptoms mainly in the aged, and those with serious medical conditions, but not in the young;[3] and

(d) establishment of infection leads to high morbidity, and a case fatality rate (CFR) approaching 15%.[1]

Later descriptors

After the passage of some months, the above descriptors were substantially amended. Newer indicators indicated that a SARS-Cov-2 infection can: (i) fail to cause pneumonia;[4] (ii) be causative of severe, varied and inexplicable forms of disease in the heart, kidney, or brain;[4] (iii) involve secondary lymphoid organs;[5] (iv) cause severe disease in young individuals;[6] (v) cause hospitalization of individuals who have no known, or identified, pre-existing health conditions, with over sixty percent of those hospitalized falling in this category;[7] (vi) be asymptomatic, or mildly symptomatic;[8] (vii) have a CFR in the low single digits;[9] (viii) involve thrombotic complications in the microvasculature, associated with morbidity, or mortality;[10] (ix) affect black and minority ethnicity (BAME) individuals more than others;[11] (x) affect men more than women;[12] (xi) cause symptoms akin to Kawasaki disease in children;[13] and (xii) cause severe and silent hypoxemia or hypoxia in tissues, without any signs of classical pneumonia,[14] with none of these factors achieving a hundred percent penetration within any of the mentioned sub-populations.

Susceptibility

Besides factors such as age, ethnicity, sex/gender, and pre-existing conditions, additional factors such as HLA antigen types,[15] levels of exposure to the virus,[16] and overall immune status[17,18] appear to be indicative in determining susceptibility to severe Covid-19.

Interventions

No intervention is conceivable in respect of genetics, ethnicity or gender. A combination of mask-wearing, social distancing, and curfews would appear to be mitigating the spreading of infection by controlling exposure. Vaccines [working on principles ranging from the use of heat-inactivated virus (Bharat Biotech and Sinopharm) to use of infection-competent but replication-deficient adenovirus-derived production of spike protein in vivo (Oxford-Astra Zeneca, Johnson & Johnson, and Sputnik) to use of encapsulated mRNA and cell fusion-based production of spike protein in vivo (Pfizer and Moderna)] appear to hold promise in reducing morbidity and mortality. Anti-inflammatory (AI) medication has become part of the protocol of treatment, in efforts to reduce hyper-inflammation (HYPi).

Refinement of the susceptibility question

We do not yet understand what makes one person susceptible to HYPi, but another asymptomatic. Since the majority of those infected appear to remain asymptomatic, or mildly symptomatic,[8] it could be useful to identify those who are susceptible to severe disease, or death,[19] to explore scope for further intervention at the level of individuals.

THE IMPORTANCE OF THE INNATE IMMUNE SYSTEM

Two types of immune systems operate with every human being; these being the innate, and adaptive, immune systems. The two act independently but also cooperate, interlacing their cellular/molecular components and functions.[20]

The adaptive immune system is too slow, and suppressed by the virus

The adaptive immune system which gives rise to antibodies is slower in responding, but more accurate and specific to pathogens,[17] taking 1–3 weeks to respond to new pathogens (or antigens) and > 1 week to reactivate pre-existing immunity. It is thus useful for slowly-developing diseases in which patients cannot die before antibodies are generated. With SARS-Cov-2, severe disease can develop within a week of infection.[4] Thus, the adaptive immune system is good from the viewpoint of vaccination, in those who have not yet been exposed, as well as in those who have been exposed without serious consequences, but it cannot help those who develop severe early disease. Even more importantly, cytotoxic (CD8+) T cells and natural killer (NK) cells are "exhausted" and non-optimal in efficacy during a SARS-Cov-2 infection,[21,22] suggesting that the adaptive immune system is also substantially suppressed by an infection.

A normally-functioning innate immune system limits pathogen proliferation through acute inflammation

Unlike the adaptive immune system, the innate immune system is faster in responding, but less specific to pathogens. It uses a multitude of cell types, cytokines, chemokines, and organ- or tissue-derived secretions to mount inflammation at sites of viral entry, to lower viral loads and ensure survival of the individual until the adaptive immune response can be mounted.[18]

A normally-functioning innate immune system mounts only the necessary amount of acute inflammation

In the initial innate response, neutrophils and macrophages happen to prime subsequent responses from cytotoxic (CD8+) T cells and NK cells, including via dendritic cells.[18] The response is finely tuned, and calibrated to generate the required level of inflammation in tissues (e.g. skin, eyes, nostrils, mouth, respiratory tract, or gastro-intestinal

tract) that first encounter the virus, through homeostasis between pro-inflammatory (PI) and anti-inflammatory (AI) pathways/mechanisms involving mutually-exclusive, occasionally-overlapping, cascades and feedback loops of cells and cytokines engaged in competition for dominance. The default state is a lack of inflammation. Acute inflammation (ACUi) arises (and also abates) rapidly to destroy viruses. To facilitate this, provisions exist to rapidly amplify or attenuate PI and/or AI pathways, based on the system's sensing of requirements and sensing of the magnitude of the challenge.[23,24] The balance of PI and AI mechanisms can be affected by constant stimulation, and/or suppression, of inflammation.

A dysfunctional innate immune system displays under-reactions or over-reactions

The innate response becomes dysfunctional in two ways, through disbalance of homeostasis, involving: (i) under-generation of ACUi, due to drug-induced immune suppression,[25] primary (genetic) immune deficiencies,[26] nutrient deficiencies,[27] or exposure to environmental toxins;[28] or (ii) over-generation of ACUi, manifesting as HYPi, with tissue/organ damage.[29] The causes of the latter are not fully understood.

Hyper-inflammation, cytokine storms and organ dysfunction in Covid-19

The severity of Covid-19 owes to HYPi-based dysfunction of infected tissues and organs,[30–37] known variously as a cytokine storm, a secondary hemophagocytic lymphohistocytosis (sHLH), or macrophage-activation syndrome (MAS). Cytokine storms result from the release of certain cytokines due to infections, autoimmune diseases, or medications. In Covid-19, cytokine storms occur in virus-infected tissues, to cause HYPi.[30] It is not yet clear what causes such storms to arise. This paper proposes an explanation.

The puzzle: Is virus-induced hyper-inflammation triggered mainly when there is a certain underlying condition?

The questions at this point are the following: (I) Is HYPi entirely caused by the qualities of the virus (i.e. the quality of the seed), or are there some underlying factors that are necessary to promote its occurrence (i.e. the qualities of the soil), independent of whether such factors fall within the category of known pre-existing medical conditions, and especially with regard to whether such factors might constitute previously unsuspected, or undetected, conditions? (II) What mechanisms, if any, connect HYPi with such factors? (III) How does the virus reach tissues and organs outside the lung, or gut, to cause HYPi in other parts of the body?

PROPOSAL: CHRONIC INFLAMMATION (CHRi) CAUSES VIRUS-TRIGGERED ACUTE INFLAMMATION (ACUi) TO SPIRAL INTO HYPER-INFLAMMATION (HYPi)

Feedback loops cause CHRi to promote HYPi by compounding with ACUi

Upsetting of the PI-AI balance can involve long-term dominance of one, and long-term suppression of the other, allowing the former to enter "unchallenged" feedback-mode operation.[23,24] Large feedback loops promoting a PI milieu in CHRi could potentially facilitate runaway HYPi, during which smaller feedback loops involving thrombosis play a role. It is known that inflammation begets thrombosis.[38] It is also known that thrombosis begets inflammation.[38] Thus, feedback can create a PI milieu in which AI feedback loops fail to suppress ongoing inflammation.[38,39] Acute inflammation (ACUi) due to viral infection could cause PI feedback loops (already operating on overdrive) to overpower AI feedback loops, and thus precipitate hyper-inflammation (HYPi). Ordinarily, inflammation is of two types: acute (ACUi) and chronic (CHRi).[40] ACUi arises and abates in days in response to a transient stimulus. CHRi arises and abates much more slowly. The two share many features, however, as well as common cell types and cytokines. A small array of 10 cytokines generates ACUi (IL-1, IL-6, IL-8, IL-11, IL-16, IL-17, G-CSF, TNF-alpha, Eotaxin, GM-CSF). Out of these, a total of 7 cytokines are shared (IL-1, IL-6, IL-11, IL-17, TNF-alpha, Eotaxin and GM-CSF) with the much larger array of 21 cytokines that ordinarily sustains CHRi (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-17, TNF-alpha, TNF-beta, INF-gamma, Eotaxin, TGF-beta, and GM-CSF). Due to this overlap between cytokines used by ACUi and CHRi, ACUi can potentially arise in a body already beset by CHRi, through the additional production of only 3 cytokines (IL-8, IL-16, and G-CSF). Thus, pre-existing CHRi could be a platform (or launching pad) that allows ACUi to be launched rapidly, and also fail to abate rapidly (since AI mechanisms are suppressed in CHRi). The feedback between inflammation and thrombosis[38,39] further accelerates the ability of this process to enter "runaway" mode. We propose that this is the basis of HYPi.

Further, we draw attention to the acute phase proteins (APPs), the most well-known of which are C-reactive protein (CRP), serum amyloid P (SAP), serum amyloid A (SAA), and haptoglobin (Hp). APPs are diagnostic markers of ACUi which also help to coordinate the immune response through both PI and AI functions. Although the term "APP" is associated with ACUi, many APPs are also associated with CHRi. This causes APPs to constitute an additional group of proteins (after the cytokines) that contain members common to ACUi and CHRi, with PI and AI functions, and with the potential to affect the overall balance, in inflammation.[41] Thus, there is a possibility of the joint involvement of the PI/AI balance of cytokines and APPs in cooperatively launching an ACUi into a HYPi, when there is an underlying, long-standing CHRi.

MICROBES THAT THRIVE ON CERTAIN FOODS CAUSE CHRONIC GUT AND SYSTEMIC INFLAMMATION

Gut microbiomes promoted by certain foods/drinks are PI while those promoted by other foods/drinks are AI

Connections between diet, gut microbiomes and inflammation are described in several thousand publications. Microbes inhabit animal and human guts, and their proliferation and abundance are profoundly influenced by diet.[42–44] Plant-based food promotes growth of microbes that stimulate AI mechanisms,[45–53] particularly when one avoids foods that contain an excess of phytates, lectins, oxalates and other substances with possible adverse effects. Red meat-based food promotes growth of microbes that stimulate PI mechanisms,[54–81] especially when consumed in the context of fried food and nitrosylated compounds, and to the exclusion of all plant-based and green/leafy accompaniments and salads. Alcohol promotes gut and liver inflammation.[82–107] Gluten leads to chronic inflammation of both celiac and non-celiac varieties,[108,109] with the latter affecting a higher fraction of the US population (6%) than the former (1%).[110] High intake of sugar leads to a PI gut microbiome,[111] although disagreement remains about whether fructose is more PI in character than either glucose, or sucrose.[112] Certain polyunsaturated fats stimulate PI mechanisms, whereas certain saturated fats stimulate AI mechanisms; however, it must be noted that some fats, such as the omega-3 fatty acids (which are polyunsaturated) stimulate AI mechanisms, and that some animal-derived long-chain fatty acids (which are saturated) stimulate PI mechanisms.[113] This suggests that attention is required to be paid both to the specific types of fats that are consumed in modern lifestyles, and diet, and to individual fats and their specific AI- or PI-related properties. PI foods cause chronic gut dysbiosis associated with increased gut permeability, when their inclusion in the diet is not balanced by (1) a suitable amount of AI food, with the balance of diet weighing-in on the side of such AI foods, and (2) lifestyle factors such as exercise. Notably, anxiety also contributes to increased intestinal permeability, through a mast cell-dependent mechanism activated by psychological stress.[114,115] CHRi caused by any of the above factors can remain undetected for years, or progress to conditions such as irritable bowel syndrome, inflammatory bowel disease, and leaky gut syndrome, or manifest as cardiovascular disease, diabetes mellitus, non-alcoholic fatty liver disease, certain forms of cancer, chronic kidney disease, or autoimmune and neurodegenerative disorders.[116]

It may be pertinent to mention here that, theoretically-speaking, sub-acute and undetected CHRi in the gut could also result from mild systemic and gut allergic responses to milk-lactose, milk-protein, eggs, soyabean, seafood, or other allergenic foods. However, in most cases, these substances cause severe and identifiable allergies (rather than sub-acute and chronic reactions). Since acute food allergies are easily identified, and allergy-causing foods are voluntarily avoided by those who display allergies, such allergic inflammation, or ALLi (which constitutes a fourth class of inflammation; beyond CHRi, ACUi and HYPi) is unlikely to be relevant in the context of an individual's exposure to SARS-Cov-2.

Therefore, if one were to discount for florid food allergies, could silent CHRi driven by food then turn out to be the fundamental underlying pre-existing condition that predisposes humans to severe Covid-19? If this were the case, florid medical conditions (due to CHRi) could be the proverbial tip of the iceberg, while undetected, asymptomatic gut/systemic CHRi could make up the bulk of the iceberg. Could attention to diet influence the severity of Covid-19, if contracted, or even be useful as a preventative measure? There is evidence that a change of diet can lead to a rapid alteration of the constitutions of gut microbiomes in a matter of days/weeks.[43]

Perhaps a change of diet, from a PI diet to an AI diet (characterized by a greater inclusion of CHRi-suppressing AI foods, and avoidance of CHRi-promoting PI foods) could work to rapidly reduce an individual's susceptibility to developing severe Covid-19, following exposure to the virus, or infection. If a change of diet could prevent HYPi, the body could run its normal course of an initial innate immune response (in the form of an ACUi, developing rapidly and also abating rapidly) followed by an adaptive immune response (i.e. development of antibodies). This possibility is summarized in Figure 1

Pro-inflammatory gut microbiota compromise tissue-blood barriers to promote body-wide dissemination of endotoxin, cytokines and viruses

PI microbes cause breaching of mucosal/cellular barriers separating the gut's lumen from the vasculature infiltrating its wall.[29] CHRi elicits gut leakiness.[117] Gut leakiness too elicits CHRi.[118] Proteases degrade tight junctions between cells in the gut's lining, once colonic mucosa is compromised by a PI milieu,[119] with PI cytokines further increasing permeability, and dysbiosis, leading to circulation of bacterial lipopolysachharide (LPS) or endotoxin that further dysregulates the immune response. Gut dybiosis is associated with altered abundances of short-chain fatty acids (especially butyrate) that seal the gut and dampen immune responses. Many diseases predisposing to covid-19 severity/fatality are associated with decreased butyrate (decreased alpha diversity),[120] and increased transcellular and paracellular hyper-permeability.[121] This suggests that it is critical for butyrate-induced sealing to keep pace with breaching of the gut-blood barrier, to stop episodic leakage from the digestive system into the circulatory system. A PI milieu created and maintained in the gut prevents such regeneration, and helps to maintain a PI milieu in the entire body (i.e,. helps to maintain a systemic state of CHRi). This leads to breaching of the tissue-blood barriers in various other organs (e.g. lung, liver, kidney, or brain), offering an explanation for how SARS-Cov-2 reaches other tissues, since SARS-CoV-2 anyway reaches the gut through the alimentary canal, causing viral RNA to be present in fecal samples.[122] SARS-Cov-2 infects gut enterocytes,[123] and causes alterations in gut microbiota in Covid-19 patients.[124,125] Therefore, guts that host CHRi due to diet can better host SARS-CoV-2 and leak it to other tissues through formation of giant syncitia,[126] and

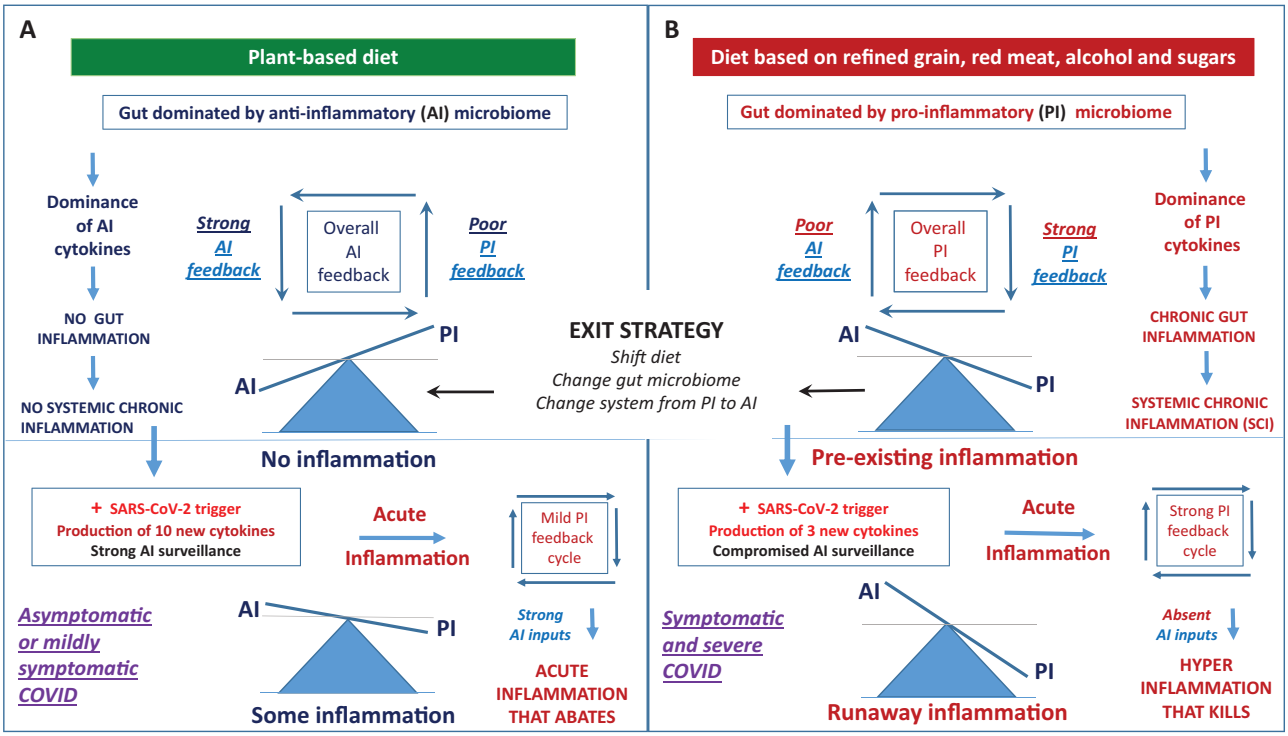

FIGURE 1 Proposed progression of events relating diet to disease outcome. *Panel A*. The top half of this panel shows that a plant-based diet promotes an anti-inflammatory (AI) feedback cycle, and leads to the setting up of an AI milieu that is then associated with a lack of any gut and/or systemic chronic inflammation (CHRi). The bottom half of the same panel shows that there is a typical (rather than an over-the-top) virus-triggered acute inflammation (ACUi), upon infection, which arises with difficulty but abates with ease because it occurs in an overall AI milieu. The end result of infection is thus a mild overall inflammatory outcome, with no hyper-inflammation (HYPi) seen. *Panel B*. The top half of this panel shows that a diet based on refined grain, red meat, alcohol and sugars, promotes a pro-inflammatory (PI) feedback cycle, and leads to the setting up of a PI milieu that is then associated with gut and systemic CHRi. This predisposes individuals to gut dysbiosis and leakiness. The bottom half of the same panel shows that there is thus an over-the-top, and out-of-control, virus-triggered ACUi, upon viral infection, that both occurs more easily and abates with more difficulty, because it occurs in an overall PI milieu that is characterized by a pre-existing chronic inflammation which desensitizes and suppresses AI mechanisms and pathways. The end result of infection is thus a sustained ACUi that transforms into HYPi characterized by a storm of cytokines and cells. Such HYPi, occurring in a PI milieu, gives rise to more organ dysfunction, morbidity and death. *Panel A* and *Panel B* are connected through a proposed exit strategy. Through this strategy, a PI milieu can be transformed into an AI milieu through adoption of a more plant-based diet, in a matter of days/weeks, to try and shift the outcome of infection towards milder inflammation and better disease prognosis. It is proposed that adoption of this exit strategy could provide a route out of the pandemic, at least until universal vaccination is feasible and effective against all present and future strains of SARS-Cov-2.

transcellular and paracellular hyper-permeability facilitated by infection of enterocytes.

Connections between obesity and inflammation, and obesity and Covid-19

Evidence is emerging that obesity predisposes individuals to developing severe Covid-19, and to poorer prognosis upon contracting a SARS-Cov-2 infection,[113,127–132] including amongst those who are young. In the context of this paper and its focus on pre-existing CHRi in individuals, it must be noted that there is an intimate connection between obesity and CHRi. Obesity gives rise to inflammation, and inflammation also gives rise to obesity;[133–135] the reason being that adipocytes secrete PI cytokines that promote further adipocyte growth, giving rise to a feedback loop that leads to increase in CHRi once obesity sets in, with involvement of the liver, and of the acute phase proteins, in this feedback loop.[136] It seems likely that this is related to nutrition, diet and lifestyle.

Thus, obesity could be considered yet another pre-existing condition predisposing to severe Covid-19, when associated with CHRi, like the many other chronic conditions such as hypertension, hyperglycemia, and certain forms of cancer that are associated with CHRi; however, the key underlying condition would still remain the basal CHRi in the gut and entire system. Our view is that systemic CHRi (S-CHRi) must be considered the main pre-existing condition that predisposes an individual to severe Covid-19, because S-CHRi can remain un-manifested and asymptomatic for years before it manifests as a florid or detectable medical condition. All of the explicitly-present pre-existing medical conditions could thus just be the tip of the iceberg predisposing individuals to severe Covid-19. CHRi could thus constitute the entire bulk of this iceberg which remains hidden from view.

Other recent relevant literature

A preprint of the very first version of this paper (revised thrice, and now in its fourth edition, during consideration for publication in this journal) was uploaded on Research Gate (DOI: 10.13140/RG.2.2.17723.44323), concomitantly with the first submission, on May 16, 2020. At that point of time, there were only three papers (e-published during April or May, 2020) that mentioned the possibility of a link between diet and Covid-19, in passing.[137–140] During the 13 months that have passed since, numerous other papers have also noted connections between Covid-19 and diet, nutrition, microbiomes, dysbiosis, immunity, or inflammation,[141–150] including one paper that happened to cite the original preprint on Research Gate.[151] However, none of these earlier, or subsequent, papers explicitly holds chronic inflammation (CHRi) to be the cause of the proposed rapid rise and slow abatement of acute inflammation (ACUi), or the proposed spiralling of ACUi into hyper-inflammation (HYPI), as proposed in this paper. Therefore, the mechanistic insights outlined in this paper provide the first "end-to-end" explanation of the entire chain of causality connecting: (i) dietary habits to microbiome constitutions; (ii) microbiome constitutions to undetected gut CHRi and dysbiosis; (iii) undetected gut CHRi and dysbiosis to undetected widespread systemic CHRi; and (iv) undetected widespread systemic CHRi to susceptibility to developing Covid-19, and especially to susceptibility to severe disease in the form of HYPi, associated with thrombosis, organ dysbiosis and death. This proposed chain of causality holds CHRi driven by diet to be the main culprit and predisposing factor (amongst those with no known pre-existing medical conditions) for severe Covid-19.

A SUMMARY

Many humans host undetected chronic inflammation (CHRi), including chronic gut and/or lung inflammation, or widespread systemic inflammation, owing to their dietary and other habits, and also owing to their living in stress- and pollutant-laden physical, or chemical environments. This could predispose such humans to hyper-inflammation (HYPi) in the form of cytokine storms. It could also predispose them to organ dysbiosis and systemic organ HYPi associated with the leakage of materials (including SARS-Cov-2 itself) across tissue-blood barriers, leading to body-wide cytokine storms and thrombosis preceding any possible activation of an adaptive immune response to the virus. CHRi could thus potentially be the main determinant of susceptibility to severe Covid-19. CHRi could probably also be reduced through a shift of diet to foods that actively promote maintenance of a gut microbiome dominated by bacteria that curb gut, lung and body-wide inflammation, instead of promoting it. Records available with hospitals and health ministries could help to explore further correlations between diet and death, or morbidity, in Covid-19, given the known connections between diet, obesity and inflammation. Also, prospective controlled studies could be conducted to verify the benefits of anti-inflammatory (AI) diets and gut microbiomes in curbing HYPi associated with viruses such as coronaviruses and influenza viruses. Notably, one such study that supports the contentions made in this paper has already appeared in the literature (150).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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