COVID-19 and nutriceutical therapies, especially using zinc to supplement antimicrobials

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Received: 8 October 2020 / Accepted: 25 October 2020 / Published online: 16 November 2020
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Abstract
The nutritional status of a patient can be critical for the efficacy of other pharmaceuticals, especially organic antibiotics, to treat viral pandemics. There may be political and scientific difficulties in achieving a constructive synergy of nutritional and prescribed allopathic remedies. For adequate treatment, timelines may need to extend well beyond eliminating viral proliferation, e.g., with vaccines, to include the goals of (a) reducing post-viral fatigue, (b) promoting earliest recovery, and (c) future resistance in often poorly nourished patients, e.g., obese (!). Many trace minerals (TM) and vitamins may need to be replenished. This review focusses only upon zinc to illustrate some problems in rectifying these TM deficiencies affecting the balance between continued ill-health (‘illth’) or regaining optimal physical and mental wellbeing. Ultimately, this is a matter of behaviour, lifestyle, and informed choice(s). See Hetzel and McMichael 1959.

Keywords
SARS-2 · Hydroxychloroquine · Ivermectin · Transdermal zinc supplements · Drug-nutrient synergy · Post-viral fatigue

Abbreviations
‘Anti-nutrients’  Dietary factors binding zinc in the gut, impeding its enteric absorption
‘Cytokine storm’  Excessive, often overwhelming, production of pro-inflammatory factors e.g. TNF-alpha, IL-1-beta, IL-6, IFN-gamma, IL-17A, etc.
ABC  ATP-binding ‘cassettes’ = intestinal cation transporters
COVID-19  Coronavirus disease (first documented in 2019) aka SARS-2
EDTA  Salts of ethylenediamine tetra-acetic acid (Versene)
HCQ  Hydroxychloroquine
IFN  Type 1 interferons (natural anti-viral cytokine)
IMN  Ivermectin (Mectizan®)
Metallothioneins  Cysteine-rich polypeptides induced by zinc or corticosteroids acting as ‘buffers’ against toxic metals (Cd, Pb), alkylating agents, etc.
Phytic acid  Inositol hexaphosphate
SARS  Severe acute respiratory syndrome (see COVID-19)
TM  Trace metals, especially iron, zinc, and copper
WHO  World Health Organisation
ZMG  Zinc monoglycerolate (Glyzinc™)
ZUFA  Zinc salts of medicinal polyunsaturated fatty acids

To the memory of Carl Pfeiffer (1908–1988), an American pharmacologist turned psychiatrist who explained why zinc and other trace elements were so important for mental health (Pfeiffer and Bravermann 1982).

“Epidemics are no accidents. A new pathogen will enter a community only when the conditions are ripe for it.”
Nathan Clumek, Brussels (Cribb 1996).

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Preamble

This commentary describes some of the problems when practising Integrated Medicine, combining the wisdom of Food Science and Dietetics (FSD) with that of experimental therapeutics. We hear and read much about the latter (it makes money), rather less about the former (FSD) and almost nothing about their synergistic interactions, except when they have adverse effects (fortunately rare)! All that may change as we try to focus on novel approaches for treating the current widespread pandemic presenting as severe acute respiratory syndrome (SARS-2) aka COVID-19. Its lethality often involves a ‘cytokine storm’ induced as an over-reaction by the host’s immune system, overwhelming the patient’s resistance. By historical standards, it is one of the lighter pandemics, but still especially dangerous for certain populations: the elderly, the obese and those lacking effective levels of Type 1-interferons.

Therapy

Since its massive outbreak in 2019 (Chan et al. 2020), a large number of drug candidates have been evaluated as possible inhibitors for this RNA coronavirus. Rather surprisingly, a few of the more promising candidates have not hitherto been classified as antivirals. They include two conventional but quite unrelated anti-infective agents, namely, hydroxychloroquine (HCQ), Plaquinil™, and Ivermectin (IMN) Mectizan®. When used with a zinc supplement, they may acquire significant anti-viral activity.

HCQ is a synthetic analogue of quinine, available since 1951 to treat malaria, a protozoal disease. It is currently used as a relatively safe anti-rheumatic and to suppress systemic lupus erythematosus (Rainsford et al. 2015). It has been derided on political grounds (Table 1) even rejected, because it does not seem to provide consistent benefits when compared between different trials. This is a very important observation, but needs some answers to ancillary and pertinent questions relating to the status of patients entering clinical trials (age, genetics, obesity, metabolic syndrome and other co-morbidities, drug clearance rates, possible dietary antagonists, etc.) and especially the nutritional and/or immunological status of the affected patients.

IMN (MK933) is used as an anti-helmintic to prevent ‘river blindness’, onchocerciasis in West Africa1 and Latin America, caused by a filarial nematode (Campbell 1989). It is the second leading cause of blindness, after trachoma. IMN is on the WHO’s list of essential medicines. It also controls COVID-19 infections when used in combination with zinc (Borody and Hazan 2020). Dexamethasone and a number of conventional antibiotics, e.g., doxycycline, clarithromycin, azithromycin, etc., have been considered for trials in COVID-19 clinics. Azithromycin may have particular advantages for use in lung inflammation and congestive conditions because of its unique ability to accumulate in lung parenchyma and mucosa and stimulate interferons (Menzel et al. 2016) [This list will probably grow considerably in the near future.] Their efficacy may also be conditioned by nutritional factors and the patient’s immunological status.

Table 1   Zinc, an adjunct therapy for viral life-threatening infections

| Some political and practical difficulties |   |
|------------------------------------------|---|
| Scepticism: It is not in the textbooks or yet been used or advocated by most opinion-leaders of allopathic medicine |   |
| The supernumerary myth: zinc is already available from Western diets, so we do not need to be too concerned if and why it may be insufficient |   |
| The non-inquisitive mindset: some trials have indicated that hydroxychloroquine is not effective, so that is the end of the story, i.e., this ‘non-result’ is accepted without criticism or reservation |   |
| Regulatory agencies and drug propagandists tend to discourage polypharmacy involving natural remedies |   |
| Being a natural remedy, zinc cannot be readily patented. The consequence is little or no action by, or support from, the originators of most new medical remedies |   |
| Misinformed mindset (‘blindset’). Since the US president, D Trump, extolled hydroxychloroquine, it must be ‘wrong’, so suggesting its use with zinc is even more unacceptable!! |   |
| Consequent censorship on Twitter, YouTube, Facebook, and elsewhere*, further promoting ignorance of scientific understanding and positive reports |   |

Comments: (i) Once again, political ignorance or following the crowd can trump wisdom (Whitehouse 2020a), even that of D Trump. (ii) The timeless Biblical admonition: “Do not spread false reports” (TNIV 2005) is just as applicable to electronic media as for vocal communication

*Even in the Australian federal parliament in Canberra

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1 Where it has been donated free of charge by Merck & Co, USA for distribution by the Christian Blind Mission and other international aid organisations.
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Zinc status

This has often been neglected (Table 2) in treating patients or adjusting their therapies, not only for treating COVID-19 but many other disorders needing more adequate nutritional support. Zinc deficiency is associated with aging (Prasad 1993) and a wide range of medical disorders (n≥22), congenital birth defects (n≥15), and degenerative diseases of all age groups (Wallach and Lan 1999). In the context of the COVID-19 pandemic, zinc repletion may be essential for:

i. (Intrinsic) anti-viral activity (Chasapis et al. 2012; Read et al. 2019; Skalny et al. 2020)

ii. Moderating the host’s response, the cytokine storm, e.g., inhibiting the biogenesis of TNF-alpha and IL-1 beta (Prasad et al. 2011).

iii. Stimulating early recovery in dual roles of (a) helping combat post-viral depression through some known—and other still unknown—effects on the brain (Pfeiffer and Banks 1982) and the immune system; and (b) repair and restoration of function, especially in the lung; zinc being an essential nutrient for renewed nucleic acid and protein synthesis.

iv. Strengthening host resistance by replenishing depleted zinc reserves in the liver, circulating leukocytes and skeletal tissues.

Chloroquine (and HCQ) may support these activities acting as ionophores assisting (a) zinc distribution to critical responsive sites in the body’s tissues and (b) perhaps also withholding zinc from replicating intracellular virus articles. Other zinc-binding molecules, particularly thiol such as N-acetylcysteine (but not d-penicillamine), might be useful adjuncts during intensive therapy.

Obesity

Many clinicians have observed the high mortality from COVID-19 in their obese patients (Popkin et al. 2020; Rebello et al. 2020; Richardson et al. 2020; Sanchis-Gomar et al. 2020; Lockhart and O’Rahilly 2020). Over 80% of obese people may compulsively over-eat caused by chronic hunger as their bodies seek essential dietary minerals, lacking in their normal, but impoverished diet. [This is known as ‘pica’ (Latin for ‘magpie’) = an abnormal craving for clays, soils from termite mounds (sic) and other sources of essential trace minerals, e.g., iron, zinc, etc.] This geophagy or geopharmacy is extensively practised by impoverished pregnant women in the Third World (Root-Bernstein 1997; Kambunga et al. 2019). It is a testimony to the need for mineral supplements to support health and combat malnutrition.

Zinc supplements may reduce the weight, body mass index, and waist and hip circumference in obese individuals (Khorsanda et al. 2019). From this limited database, two lessons seem to be (1) effective zinc repletion can overcome previous zinc depletion, often chronic before the pandemic but enhanced by rapid viral proliferation; (2) it may take time to adequately restore/renormalise the body’s zinc reserves.

A considerable proportion (≤25%) of COVID-19 patients in recovery phase suffer prolonged post-viral symptoms including mental distress (Garner 2020). Sustained zinc repletion may be needed during this non-lethal second phase of the pandemic.

Table 2 Some problems (and queries) about using zinc in crisis medicine

- Recommended daily intake (RDI) for zinc is 12–15 mg taken orally. For crisis medicine, 200 mg/day has been used in tandem with other anti-infective agents (hydroxychloroquine, ivermectin, etc.)
- Estimated efficiency of intestinal zinc absorption from normal diets may be as low as 20%. This inefficiency is due to inhibition of zinc uptake by a) anti-nutrients, e.g., phytic acid, other polyphosphates, even phosphoric acid (added to soft drinks); b) copper or iron (II) competing with zinc for uptake by intestinal ABC transporters and c) metal chelators added to processed foods to prevent copper- or iron-induced rancidity, e.g., EDTA; unfortunately also complexing zinc (‘collateral damage’)
- There is little information about zinc bio-availability when using such ‘super-doses’
- For how long can they be used without overtaxing zinc detoxicant/excretion mechanisms or inducing profound copper deficiency?
- Does surplus unabsorbed zinc from such super-doses compromise the symbiotic commensal ‘good’ bacteria in the bowel?
- What is the effect upon normal zinc-storage mechanisms in bone, or natural sequestration by metallothioneins in the liver?
- Doses with >150 mg/day oral zinc supplements can be toxic (Chandra 1984; Mindell 1985; Vaughan and Judd 2003). Lower doses (25–40 mg/day) are therefore advocated (Razzaque 2020) to reduce potential suppression of beneficial immune responses
- For further discussions of zinc and its importance for human health (for human health treating viral infections), see reviews by Chasapis et al. 2012, Read et al. 2019; Derwand and Scholz 2020; Razzaque 2020; Skalny et al. 2020; Whitehouse 2020b, amongst others

Other comments

1. Concerning nutritional status:
Some facets of this commentary may apply to several
anti-inflammatory, antioxidant, and immunostimulant trace
elements, e.g., copper, zinc, selenium, other essential nutri-
ents, and many vitamins, e.g., B₆. They are all exogenous to
the body and must be efficiently ingested from the diet or
supplied parenterally.

Three quotes from Carl Pfeiffer writing 40 years ago are
still so pertinent today:

- “If only doctors were urged to participate in nutritional
guidance, if only they’d become more interested in nutrition….”
- “Orthomolecular medicine (biochemical medicine) is
simply the correction of faulty biochemistry, with the
right molecules or essential nutrients given at the right
time.”
- “A preventive program is far more effective than the use
of drugs against symptoms.” (Pfeiffer and Banks 1982)

2. Concerning early trials of alternative non-vaccine treat-
ments for COVID-19. Some conclusions from certain
recent trials of potential therapies have been sharply
criticised, their methodologies seeming inadequate and
their conclusions questionable (Bramstedt 2020). If the
dietary and immunological status of the patients were
more fully evaluated before and after the treatments, we
might find that personalised corrective therapies (e.g.,
nutritional, immunostimulant, etc.) are just as important
as prescribing any new or rediscovered anti-viral drug.

3. Planned nutrition is now becoming respectable medicine
again (BourBour et al. 2020; Polamarasetti and Martiro-
syan 2020) as it certainly was half a century ago.

4. Final suggestions. Improving the zinc status of COVID-
19 patients should help to both conquer the infection and
bolster their recovery. Other nutrients should also be
considered when adopting this health-restoration strat-

ey.

Acknowledgements We are grateful to Professor KD Rainsford for
moral support and directing attention to some key references.

Compliance with ethical standards

Conflict of interest There is no conflict of financial interest.

Appendix

- An intriguing ‘blast from the past’ is provided by two
observations on the properties of chloroquine (the
chronological precursor of hydroxychloroquine): (i)
chloroquine manifests many anti-inflammatory effects,
disclosed by experimental studies over a wide range of
in vitro and in vivo assays (Swingle 1974); (ii) a zinc-
deficiency disease in chickens presents as a form of
polyarthritis, that is corrected by administering chloroquine
(Hoekstra 1969). Even 50 years later, poultry scientists
are still very concerned about zinc nutrition as ‘preven-
tive medicine’ (Naz et al. 2016).

The journal Frontiers in Public Health has published
some important reviews including treating COVID-19
by dietary changes (Chaari et al. 2020). The companion
journal Frontiers in Pharmacology has discussed therapeu-
tic options under investigation (Kaddoura et al. 2020).

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