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COVID-19 and Immune Function–"A Significant" Zinc

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ABSTRACT

The pandemic COVID-19 is the most terrible calamity of the present human history also it has led to the worldwide issue of public health as a primary health safety problem. It was assumed that the infection of COVID-19 has two-phases, the immune protective as well as damaging phase. In the immune protective phase, clinicians try to enhance the patient immune response, and in the immune damaging phase, clinicians try to control the inflammatory immune response. Zinc belongs to the d-block or a transition element, it is an indispensable trace metal needed for vital cell activities like growth, as well as cell survival. It has significant contributions to immune homeostasis and functions; zinc inadequacy reduces primary and secondary immune responses equally. Studies have shown people who are deficient in zinc are more susceptible to infection. An inclusive knowledge of the bioavailability of the transition metal zinc will help to be aware of those that are valuable and protective for the population's health. This work is concentrated on the significance of zinc for the immune function, the presence of it's in optimum amounts and how it is beneficial to health in general and in fighting with COVID 19 in particular until today.

Keywords: Immune system, Zinc, Pandemic, Nutrition, Human-health.

INTRODUCTION

According to the WHO Director-General's opening comments at the press briefing on COVID-19 on 23rd October 2020, he said that we are at a crucial moment in this worldwide pandemic, especially

the countries situated at the northern equator like Austria, Belgium, Bulgaria, Canada, China, France, Germany, Hungary, India, Japan, Mexico, Netherlands, Norway, Poland, Romania, Russia, Spain, Sweden, Switzerland, United Kingdom, Ukraine and the United States will be the worst affected. The next couple of months are going to be extremely difficult, and unfortunately, some countries are heading on a critical path. He further appeals to the international community to take necessary and quick responsive steps and improve the fundamental health services, to avoid preventable death. Still have time to turn the tide. The threat of additional Second, third and fourth waves of coronavirus will remain until widespread immunity to the corona virus is feasible, a problem that is compounded by the difficulties in manufacturing and distributing a vaccine[1,2]. Millions of people in the whole world are affected by the coronavirus and more than a million died now.

COVID-19 is crown-shaped, having a diameter of about 600-1400A0, RNA virus. It has a larger binding interface, with one side con-cave faced in addition to more associate with Angiotensin-Converting Enzyme 2 or ACE2 "receptor" and has a major intimacy to associate by means of the N-terminal helix of ACE2[3]. It is a respiratory disease, transmitted via the droplets from coughs and sneezes of an infected person and enters by inhaling through the nasal system and initiates reproducing. ACE2 is the key receiver for the COVID-19 virus[4].

Human immune system and its working mechanism

The human body has an immune system that safeguards against diseases, germs, from malignant cells and has played a major role to preserve wellness. The white blood cells lead the defense mechanism in the human body which is present all over the body through arteries. To screen for attacking microbes, the body allows the lymphatic system by exchanging cells and fluids within the blood and lymphatic vessels, which carrying lymph. Every lymph node has proper compartments everywhere they be able to combat antigens. The immune cells accumulate, operate and help to encounter antigens present in the nodules of the spleen and the lymph nodes[5-8].

For COVID-19, a proper medication or vaccine could not be available till now, so the body's immune system or natural defense is considered the best mechanism to support and defend against it. The human body has three kinds of immunity (a) innate immunity, (b) adaptive immunity and (c) passive immunity; everybody have natural immunity. The adaptive immune response is acquired in a lifetime when an organism is exposed to the environment and pathogens. Passive immunity exists as immune products are introduced into the body. It categorized as : body acquired natural immunity as of the motherly side and artificially it is obtained from medicine like antibodies that given to cure or prevent diseases[9,10]. The natural defense mechanism defends from all kinds of infections and pathogens[11-13]. Although, once the body experience attack of germs or viruses, the immune system will inactivate and expel the invading pathogens. When the immune system is unable to operate properly, the infection can have health effects. This situation is also happening with the COVID-19 as well[14].

Once the immune system's cells are vulnerable to disease causing pathogens, they try to kill the invading pathogen and complete their assignment by interaction with the central and peripheral lymphoid organs via blood to reach the injury sites. Blood flows throughout the body, and is a carrier for naïve and antigen, when immune cells exposed over the site of their location to the site of infection or injury, it acts as a means of interaction for immune system. After penetrating into the bloodstream the immune cells and transported to tissues all over the body upon leaving the lymph nodes in the interconnected intricate network of lymphatic vessels. A variety of molecular and cell profiling attempts are available to study the human defense function. With the innovation of instruments like polychromatic flow cytometers and the advancements within genomics and pro-teomicsand other technological advancement have as well take placed, generating a sole capacity in the field of population health and diseases. Due to inherent heterogeneity in human studies realized that more samplings are needed to be analyzed in a limited time[15]. Afterward infection with pathogenic microorganisms, the immune system responds to mediate antibody production against the pathogen. The T cells assisted the B cells to be distinguished over plasma cells and memory cells, plasma cells generate antibodies precise to a viral antigen. The neutralizing nature of antibody is effective in obstructing the virus as of penetrating into healthy

host cells. This limits the disease and has a strong defensive function at the next phase of infection. Antibodies in circulation and memory cells prevent relapse of the infection. Cell-mediated immunity reaction maybe noticed within the infected cells mounted by circulating T-lymphocytes. In general adaptive immune reaction is addressed via helper T cells Cytotoxic; also T cells take an important part during the removal of the viral-infected host cells[16]. The details collected on the basis of research on SARS-CoV and MERS-CoV can provide to looking at further information to be aware of, how SARS-CoV-2 outflows the host's immune response since information on SARS-CoV-2 still restricted. Particularly, considering the succession similarity data which shows 80% of the RNA series of SARS-CoV and 50% of the RNA series of MERS-CoV agree with the RNA of SARS-CoV-2[17], in addition to these SARS-CoV-2 displays novel genomic regions. In comparison between SARS-CoV and further associated coronaviruses, its S protein is 20–30 amino acids longer. Thus, SARS-CoV-2 can be postulated to have comparable immune evasion approaches. However, other mechanisms of host interaction remain unexposed[18,19].

Shi *et al.,*[20] suggested several basic strategies based on a clinical rational approach for the management of patients with COVID-19. It was assumed that the infection of COVID-19 has two-phases, the immune defense-based protective phase and the inflammation-driven damaging phase. During the early days, clinicians must try to enhance the patient immune response and during the next stage, they should try to repress the inflammatory immune response. Being a very much lung-protective, Vitamin B3 needed to be served immediately once the coughing starts, upon the start of breathing complexity, hyaluronidase may be provided intratracheally and at the same time, 4-MU may have utilized to contain HAS2. Obviously, susceptibility information has to be given by HLA typing for strategizing inhibition, management, vaccination, and clinical methods for the management of the disease.

Importance of zinc in immune development

Zinc is an indispensable micronutrient needed during essential cell operation like cell growth, as well as Survival[21]. Zinc paucity has been associated with depression of immune function. Zinc influences cellular activities and cellular function. Zinc is associated with modulating signalling pathways of immune systems. Mechanisms of the Zinc-mediated modulation of immune function control are still vague. Have increasing indications that Zinc acts as a signalling molecule[22]. Zinc facilitates transduction of a various signalling cascades in reaction to stimuli received from extra cellular environment. Homeostasis of Zinc in human body is highly controlled[23]. Zinc transporters and metallothioneins proteins regulate the chemical kinetics of Zinc in human body. Immuno deficiency is caused by the disruptions of a Zinc-signal axis[24]. Zinc has important role in immune homeostasis and functions; zinc deficiency reduces equally primary and secondary immune responses. That's imperative to study Zinc signalling in different cell types. Studieshave provided insights into the molecular details of Zinc function in the immune system. The nutritional deficiency has been found associated with functions of equally innate and adaptive immunity[25]. Physiological significance of zinc is reflected in current computational. Recently researches have shown that about 10% proteins of entire human genome be able to potentially attach Zinc with Zinc finger motifs[26,27]. All of these proteins are known to have important role in basic cellular activities; thymic atrophy and lymphopenia is induced by zinc deficiency. Zinc deficit impairs host defence through neutrophils and natural killer cells; cytokine production. These basic cellular dysfunctions are caused by deregulation of cellular functions. Like replication and transcription[28,29].These alterations can result in an augmented infection susceptibility. Zinc also is cofactor for different enzymes; recent studies have exposed the role of Zinc's as a second messenger[30-32].

Zinc transporters in human system

Zinc is an abundant metal, distributed all over in the human body. Dietary Zinc is absorbed by Zinc transporters in intestines[33,34]. Circulating Zinc has resumed into cells as well as is circulated in cells with the help of Zinc transporters and metallothioneins. Loss-of-function of zinc transporters due to mutation is associated with autosomal dominant myopia[35].Genetic alterations can affect zinc transporters. Genetic alterations are associated with osteoarthritis schizophrenia. Genetic changes have been associated with less liver regeneration and decreased insulin signalling. Zinc deficiency has

also been associated with parkinsonism-dystopian and neuro degeneration. Experiments of disruption of zinc transporters with mice have exhibited embryonic lethality. In mice models a targeted interference with zinc transporters causes severe zinc deficit in baby mice as Zinc content of breast milk extremely low[36-38]. This observation is important as same condition can cause similar symptoms in humans with modifications in zinc transporters

Signalling and Zinc Transporter

Zinc is known to modulate the function of myriad molecules like neurotransmitter hormones, growth factors, and cytokines. Zinc regulates the protein functions by bringing conformational changes in their conformation[35]. Zinc behaves as a second messenger in allergic responses. Upon sensing an antigen mast Intra cellular granules containing histamine are released by mast cells to initiate an allergic response[39,40]. The Zinc release depends on calcium influx cascading reactions then followed and Induce inflammatory cytokines genes[41]. Zinc transporters are highly expressed in mast cells. Zinc transporters are up regulated by antigenic stimulation. Immune modulation by zinc also causes translocation of protein kinase-C to membrane, which induces production of interleukin-6 and tumor necrosis factor alpha. Recent studies have shown Zrt/Irt-like protein-10 make a heteromeric complex with Zrt/Irt-like protein-6. Zinc also controls epithelial mesenchymal transition through E-cadherin down regulation in zebra fish embryos[42]. Zinc uptake regulates bone morphogenetic changes by affecting the signalling of growth factor beta protein. Zinc transporter family suppresses phosphordiesterase activity to preserves AMP levels in hormone G-protein coupled receptor signalling, which is central pathway for hormonal control. As a whole, such observations show so as to Zinc transporters make definite Zinc signalling axes to selectively shape discrete signalling events intra cellularly[43,44].

Zinc modulation of Adaptive Immunity

Zinc deficiency has multifaceted impact on human immunity. Deficiency of zinc resulting in increased vulnerability to infections. Chronic dysfunctional inflammatory responses are also reported in zinc deficiency. Zinc supplementation can improve human immunity[45,46]. Zinc is important in normal immune-cell homeostasis. Zinc has important role in specific immunity and innate immunity. Different cell type growth and development is affected by zinc cells like T cells and B cells that permit crosstalk amid the innate and adaptive immune reactions. Antigen presenting cells differentiates from hematopoietic stem cells. Antigen presenting cells are imperative in connections of innate and adaptive immune reactions. In this process, antigens are degraded into peptides, loaded onto major histocompatibility complex II, to antigen specific CD4+ helper T cells to initiate immune reaction. During the maturation process of immune cells, Zinc transporter expression leads to net decrease intracellular zinc content[47]. Microscopic investigation exposed that Zinc enables MHC-II endocytosis and obstructs the transferring of MHC to bio membrane. Reduction in cellular Zinc is needed in MHC-II antigen presentation. Zinc deficiency can also lead to skin inflammatory diseases can also occur[48,49]. The number of epidermal dendritic cells, Langerhans cells is significantly reduced in zinc deficiency. Clinical improvements have been seen with oral Zinc supplements[50]. This may occur due to the depletion of Langerhans cells. Th1 responses are involved in autoimmune diseases. Excessive Th2-type immune responses have been associated with chronic allergic inflammatory diseases like asthma. T cells have two categories CD4+ Th cells and CD8+ Cytotoxic T cells. Adaptive immune response cells provide immunological memory to effectively encounter disease causing organism that has been beforehand encountered. This is secondary immune response. Th-cells are linked to autoimmunity CD4+ T-cell subsets produce different patterns of cytokines. T cells reach mature in thymus finally leaving the thymus to run in circulation[51,52]. Zinc deficiency causes thymic atrophy. In model organisms zinc deficiency causes decline in mature T-cell. In vitro apoptotic studies have demonstrated more lymphocytes and thymocytes apoptosis in zinc-free medium as compared to medium with added zinc[53]. Thymulin modulation by zinc is another plausible mechanism for thymic atrophy. The reduced activity of Thymulin has been linked to zinc deficiency. Thymulin is secreted by thymic epithelial cells which bind on T cells to promote T-cell maturation. Serum Thymulin activity has been found to improve by Zinc supplementation suggesting that Zinc helps in formation of functional peptide. Microarray analysis has shown that. Zinc deficiency has been involved in expression of 1,200 genes in mice linked to the immune cell functioning. Thymulin Zinc is central for T-cell proliferation in

response to cytokines and mitogenic agents Zinc controls the Th1/Th2[54]. Zinc affects components of the T-cell receptor signalling pathway. Zinc deficiency suppresses the production of cytokines such as IL-1, IL-2 and IL-4. In mice experimental autoimmune encephalomyelitis and collagen-induced arthritis models, zinc treatment prevents T-cell-mediated immune responses. Nutritional Zinc is important in development and maturation of helper T cells. B cells develop initially in the bone marrow are important part of humoral immune response[55]. Mature B cells are antigen-presenting cells. Antigen presenting cells load antigenic. Peptide fragments onto MHC-II for presentation it to other immune cells. In immune reaction, B cells that are activated undergo massive clonal multiplication with somatic hyper mutation in immunoglobulin genes to obtain a high-affinity Immunoglobulin. The zinc transporter family member 10, is a cell membrane localized transporter in splenic B cells. Transports Zinc from the fluid around cells, Interruption of this transporter antigen presenting cells, including B cells that are mature, lessens antigen specific antibody responses. Production of Igg antibodies impaired B cell receptor signalling is also involved. B cell receptor signalling works through multiple pathways mediate cell activation, proliferation. Zinc has a negative impact on protein tyrosine phosphatase affecting B-cell receptor signalling. Zinc negatively regulates oxidants which can suppress Protein tyrosine phosphatase activity. The involvement of oxygen radicals in B cell receptor signalling as a second messenger has been documented. B cell receptor engagement stimulates reactive oxygen species production, which inhibits Protein tyrosine phosphatase amplifying B cell receptor signalling. Zinc transporter protein family member 10 deficiencies pointers to damage of mature B cells and a noticeable loss of the antibody reaction. This protein is not a chief provider to intracellular Zinc homeostasis, but somewhat set the onset of B cell receptor signal power by locally moving Zinc. Immunological recollection, which includes memory B cells and long-lived plasma cells, is principally produced from side to side by germinal centre reactions. Zinc is important for cellular function and maintenance. Hence, secondary responses to earlier come across antigens are weakened in zinc deficit[56]. Zinc deficient environment significantly weakens germinal centre. These reports with animal models point to the impaired signaling through B cell receptors in the mature B cells. Therefore, immune memory cannot be properly produced in these animals. Early B-cell growth is unfavourably affected by zinc deficiency mice fed with zinc deficient diet show a 50% failure in pre-B cell populations and 25% failure in juvenile B-cell populaces[57]. Steroid-implanted mice have condensed numbers of juvenile B cells in the bone marrow. The effects of zinc shortage on early B-cell development are due to the effect of glucocorticoids as in T cells. Chelation Zinc inside cell by N, N, N, N-tetrakis (2-pyridylmethyl) Ethylene diamine persuades apoptotic cell demise of mature B cells. Zinc transporter proteins are highly expressed on the exterior of pro B cells as compared to mature B cell[58]. Zinc transporter member 10 signalling inhibits the apoptosis encouraged by activated caspases and encourages pro-B-cell survival. Zinc transporters are also strongly expressed in acute myeloid leukaemia. Cytokine stimulation activates the Janus kinase-Signal transducers and activator of transcription which further induces zinc transporter gene expression and leads to zinc transporter mediated signalling. In this way, Zrt/Irt-like protein family member 10-Zinc signalling may control fate decisions in lymphocyte Forebears in physiological process for B-cell development which guarantees functionality and inhibit auto reactivity[59]. Majority of afresh nascent B cells are eliminated through apoptosis. Deficiency of zinc effects the gene expression of the BCL/BAX family of proteins. Nonreactive or auto reactive B cells through the developing course are eliminated by down regulation of these signalling pathways and have been found over expressed in follicular lymphoma. Since zinc transporter protein deficient immature cells display poorer inside cell zinc level it can be inferred that zinc role may be synchronized by these anti apoptotic factors in maintenance of healthy B cell populations, B lymphocyte homeostasis and occupation[60,61].

Zinc intake recommendations by life stage and gender

Zinc is a d-block element, belongs to Group-2B in the Periodic table besides Cadmium (Cd) and Mercury (Hg). Its electronic arrangement is $3d^{10}4s^2$. Zinc has the only one oxidation state +2 (Zn^{+2}). It's important ores are sphalerite (ZnS), zincite (ZnO), franklinite [ZnO (Fe, Mn)$2O_3$], calamine [$Zn_2(OH)_2$ SiO_3] and smith stone ($ZnCO_3$) on average have 5–15% zinc. The Zinc (Zn) is indispensable to life;

and next to the commonest trace metal, a total of 2-3 g in the human's body and nearly 90% is found in muscle and bone. It is a vital element parts of several enzymes that taking part in the synthesis and degradation of proteins, carbohydrates, lipids and nucleic acids and in the metabolism of supplementary micronutrients. It also stabilizes the structure of cellular components and membranes, also involved in the preservation of cells as well as the integrity organ. It is a part of various systems and biological reactions and mainly required for the appropriate growth, immune function, and maintenance of the human body and many more. Paucity Zinc leads to too many health problems including slow growth, lower insulin levels, loss of appetite, irritability, loss of hair, and dryness in skin, slowed the healing process, weak taste and smell sense, diarrhea and much more. Moderate zinc paucity leads to intestine disorders which hamper food absorption, alcoholism, kidney failure and chronic debilitating diseases. Zinc may also assist in fighting against viruses, and has antiviral activity against the herpes virus as well[62-65].

Upper limits of zinc intake

It is a toxic metal after consumption of 4-8 g zinc; it has been observed as an acute symptom of nausea, vomiting, diarrhea, fever and lethargy[66].The long-term zinc consumption of more than the required amount likely to be active together by means of the metabolism of different essential trace minerals. Particularly, Copper appears to be responsive to elevated zinc intake. Zinc ingestion of 0.05 g per day influence the copper indexes status, for instance, Cu and Zn-superoxide dismutase in erythrocytes[67-69]. Poor copper levels as well as ceruloplasmin levels and anemia being witnessed a higher limit of zinc ingestion, 0.45 g per day to 0.66 g per day[70,71]. In the studies of zinc supplementation a change in serum lipid pattern with immune responsive action was noted[72,73]. The maximum amount of zinc ingestion for children and adult men is valuating at 0.023-0.028 g a day along with 45 mg a day in each case[66]. The scientific statistics of observational and experimental studies utilized to build up Dietary Reference Intakes (DRIs). The quality of studies is reviewed by examining study design; methods used for measuring intake and indicators of adequacy and biases, interactions and confounding factors. Life stages along with gender have been reviewed, but the statistics did not available to propose a ground of various needs for men and women in various age class for many of the micronutrients.

Benchmark standards categorized as-EAR (Estimated Average Requirement). The ingestion that meets the expected nutrient desires of half of the individuals in a class.

Table 1: Infants with Children

Age Group 0-6 months	AI or Adequate Intake 2.0 mg per day	
Above 6 months-one year	EAR	RDI
	0.0025g -Daily	0.003 g -Daily
1-3 year	0.0025 g -Daily	0.003 g -Daily
4-8 year	0.003g -Daily	0.004 g -Daily

For 0-6 months infants the average intake of breast milk (0.78 L per day). The absorption of zinc is higher from breast milk and the average concentrations of zinc in breast milk decrease from the first month to six months[74].

Table 2: Children and Adolescents

Age Group	Boys		Girls	
	EAR	RDI	EAR	RDI
9-13yr	0.005 g-Daily	0.006 g-Daily	0.005 g-Daily	0.006 g-Daily
14-18yr	0.011 g-Daily	0.013 g-Daily	0.006 g-Daily	0.007 g-Daily

Table 3: Adults

Age Group	Men		Women	
	EAR	RDI	EAR	RDI
19-30yr	0.012 g -Daily	0.014 g -Daily	0.0065 g -Daily	0.008 g -Daily
31-50yr	0.012 g -Daily	0.014 g -Daily	0.0065 g -Daily	0.008 g -Daily
51-70yr	0.012 g -Daily	0.014 g -Daily	0.0065 g -Daily	0.008 g -Daily
>70yr	0.012 g -Daily	0.014 g -Daily	0.0065 g -Daily	0.008 g -Daily

Table 4: During Pregnancies

Age Group	EAR	RDI
14-18 yr	0.0085 g-Daily	0.010 g -Daily
19-30 yr	0.009 g-Daily	0.011 g -Daily
31-50 yr	0.009 g-Daily	0.011 g -Daily

A normal Zinc accumulation during pregnancy periods is 0.73 mg a day. The absorption of Zinc in pregnant and non-pregnant women is the same, but about 2.35 mg/day absorption has been utilized to estimate the additional requirement of pregnant women[74,75].

Table 5: Post-Pregnancy Female or Breast feeding Women

Age Group	EAR	RDI
14-18 year	0.009 g -Daily	0.011 g -Daily
19-30 year	0.010 g -Daily	0.012 g -Daily
31-50 year	0.010 g -Daily	0.012 g -Daily

For pregnant and lactating women using a larger amount of iron supplements at the time of pregnancy and lactation, zinc absorption may decrease[76-78].

Leading Food Sources with Zinc

A variety of foods have zinc. It is found in large volumes mainly in animal foods, fish, red meat, and poultry. It exists in foods in complex form instead of free ions.

Various sources of Zinc foods that should be part of usual dietary intake showed in Table F.

DV* = Daily Value. The U.S. body of Food and Drug Administration (FDA) made DVs for the benefit of consumers balance the nutrient value of foods and nutritional supplements. Foods having 7% or further of the DV are regarded as to be good sources of Zinc, but foods are having a lesser extent of the DV as well as impart to healthy nutrition.

DISCUSSION

Til now there is no 100% effective vaccine available for COVID-19 or there possibly no exclusive antiviral therapy suggested till now. The choice treatment option is symptomatic. WHO and the different World organizations referred to the preventive guidelines to counter the pandemic and make people safe from the infection and fortify the implementation of strict safety guidelines for the prevention like as follow.

1. Keep away from direct contact with individuals affected by COVID-19.
2. Wash your arms frequently with soap, particularly after coming in contact with infected human beings or their surroundings.
3. Keep preventing the nose, eyes, and mouth from touching.
4. Always use a tissue to cover up a cough or sneeze.
5. People who can be immune-compromised should restrict themselves from public activities.

It is important to safeguard and keeping the healthy immune function in all seasons to preventing infection and disease. Zinc has a multidimensional effect on the immune system. Zinc has many important roles in our body. Zinc is a vital element that our body cannot make itself. This means we have to obtain it from our diet or supplements. People should need to know the Zinc-rich foods, and consumed foodstuff rich in Zinc for instance lean red meat, whole-grain cereals, pulses, fish, roots and tubers, green leafy vegetables and legumes, etc. The community must be conscious of their health issues. Certainly, lifestyle and dietary patterns are able to change human society's fate. It is not too late to turn the tide.

CONCLUSION

The pandemic COVID-19 is one of the worst human disasters in the world today. There is no vaccine available till now, and it remains a significant concern to international health security. People have not sufficient knowledge to fights the pandemic COVID-19. The WHO and the different World organizations referred to the preventive guidelines for people's safety. The best way to fight the pandemic, people must have to keep the immune system healthy. Strengthen to the body immune function people must have to consume nutritious foods, and making a healthy lifestyle are the most important ways. Zinc is a vital element that our body cannot make it, and play an important role to improve the defense function in our body and has multiple aspects of the immune system effects. This means we have to obtain it from our diet or supplements. It is vital for our immune system function. Diet rich in Zinc for example fruits, vegetables, nuts and seeds acts to boost public health quality and life span. Certainly, lifestyle and dietary patterns are able to change human society's fate. The optimum limit intakes of Zinc for people were found effectual.

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Conflict of interest

The authors declare that there is no conflict of interest.

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