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Lipid Therapy for Dyslipidemic Disorders Activates 21st Century Nano Antioxidant Hydrogen as a Potential Anti-COVID-19 Agent: Review.

Irina Vasilieva[1,4,5,6,7] ORCID: https://orcid.org/0000-0001-7019-4443 . **Maria Vasilieva**[1,2,3,6,7] ORCID: https://orcid.org/0000-0003-4588-2716 . **Ilie Vasiliev***[1,7,8,9] ORCID: https://orcid.org/0000-0002-8962-2927 .

[1]State University of Medicine and Pharmacy" Nicolae Testemițanu"
[2]"Nicolae Testemițanu" University Clinic of Primary Medical Assistance of State University of Medicine and Pharmacy.
[3]Laboratory of Neurology and Medical Genetics Republic of Moldova
[4]Department of Laboratory Medicine. State University of Medicine and Pharmacy" Nicolae Testemițanu"
[5] "Timofei Moşneaga" Republican Clinical Hospital, Republic of Moldova.
[6] Institute of Emergency Medicine. Republic of Moldova.
[7]World Academy of Medical Sciences, Netherlands, Republic of Moldova
[8]State Institute for Postgraduate Advanced Training of Doctors, Saint Petersburg, Russia
[9] Scientific Research Institute of Transplantology and Artificial Organs, Moscow, Russia.

*Corresponding Author: MD Ilie Vasiliev, Academy Professor at the World Academy of Medical Sciences (WAMS). First Superior Executor Vice President WAMS. Chairman of the General Council WAMS. Netherlands, Republic of Moldova. Email: ilievasiliev@gmail.com

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Immunocompromised CHAOS develops Multisystem inflammatory syndrome.

According to the World Health Organization (WHO), coronavirus infection (COVID-19, (COronaVIrus Disease 2019) is an infectious disease caused by the SARS-CoV-2 virus [1]. SARS-CoV-2 virus, Severe Acute Respiratory Syndrome-related coronavirus 2. Initially considered pulmonary - respiratory pathology, then it turned out to be poly-systemic, with multi-inflammation of many other organs, and central nervous system. Multisystem inflammatory syndrome in adults (MIS-A) [2], SARS-CoV-2 liver infection [3]. In pediatrics Multisystem inflammatory syndrome in children (MIS-C) or PMIS-TS (Pediatric MIS temporarily associated with SARS-CoV-2 infection) [4,5], SARS-COV-2/ COVID-19 in children induce Kawasaki-Like Disease [6]. Neurological manifestations [7], recurrence of COVID-19 infection with meningitis without pulmonary involvement [8]. Brain damage in COVID is primarily neurological, as a material signaling pathway of inflammatory COVID-infection of cerebral vessels. This is important, from the release of these patients, from additional stress, suffering, stigmatization in society, their isolation, intimidation, coercion (bullying) with violation and restriction of their rights. Since, concomitantly with inflammatory lesions of many organs, cognitive deficits are a component of the post-acute consequences of COVID-19 (PASC), where the role of the kynurenine pathway is significant with temporary cognitive impairment [9]. The main pathway for the breakdown of tryptophan is an amino acid, without which the synthesis of serotonin is impossible, which controls the cycles of sleep and wakefulness, which is the precursor of the sleep hormone melatonin

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In patients with COVID-19, an imbalance of T-helpers 1 and 2 leads to a cytokine storm that can contribute to myocardial damage [10]. MIS is conditioned caused by immunocompromising (IC) CHAOS - [C]ardiovascular Compromise: shock; [H]omeostasis; [A]poptosis; [O]rgan Dysfunction; [S]uppression of the Immune System with the development of Systemic inflammatory response syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS) [11,12]. With pronounced multiple and other symptoms: Electro - Ion Membrane Distress Syndrome (Syndrome Maria & Irina Vasilieva) [13,14] with membrane manifestations of electrical storm or electromembrane paralysis; Capillary Leak Syndrome; Microcirculatory-Mitochondrial Distress Syndrom [15,16]. Also described: Overlap mechanisms of transient global amnesia and COVID-19 infection [17]; Hypokalemia-stroke mimic [18]; Differential diagnosis of cacosmia and dysgeusia in COVID-19 pandemic [19].

Installed Acute Vascular Distress Syndrome entails Acute Brain Infarction, Acute Respiratory Distress Syndrome and Multiple Organ Dysfunction Syndrome

The manifestations of the severe multisystem inflammatory syndrome with COVID-19 resemble primary/secondary hemophagocytic lymphohistiocytosis as a fatal complication with the development of Waterhouse Friderichsen syndrome, similar to Sanarelly Schwartzman's phenomenon, now called, Disseminated Intravascular Coagulation Syndrome (DICS), accompanied by Acute Respiratory Distress Syndrome (ARDS) and MODS [20]. In SIRS, the cytokine storm involves peptide hyperkinetically active informational molecules of cytokines with a molecular mass of ~ 5–25 kDa: TNF α, IL_1, IFN γ, IL_6 and IL_{10} [21], which destabilizes Thrombomodulin (CD141 or BDCA-3) and the anti-inflammatory effect of protein C indirectly associated with the endothelial receptor EPCR (Endothelial cell protein C receptor). In other cases, protective cytokines aimed at destroying pathogenic bacteria, viruses, in cases of IC CHAOS dissonance, generates an imbalance between: Reactive oxygen species (ROS) / the antioxidant system (AS); reactive nitrogen species (RNS) / anti nitro oxidant system (ANOS) manifest themselves as Oxidative and Nitro-halogenic stress [22,23]. Serum from COVID-19 patients who did not survive induces oxidative stress, lipid peroxidation, and ferroptosis in human endothelial cells through a mechanism that depends on TNF-α [24]. Developing Endothelial Dysfunction, today considered as an imbalance between vasodilating, angioprotective, antiproliferative / vasoconstrictive, prothrombotic, proliferative substances produced by endothelial cells. They provide in the regulation of vascular tone and permeability, proliferation, angiogenesis, hemostasis, cell migration and nutrient metabolism, atherogenesis, thrombosis and inflammation. Acute cerebral infarction or ARDS [25] is considered as a complication of established acute vascular distress syndrome (AVDS) [26]. Vascular-pulmonary tissue is rich in ACE2 receptors, which contributes to rapid damage membranes to endothelium cells and alveocytes and the development of SARSCov2 / COVID19 respiratory failure, due to the accumulation of cytokine storm mediators. Along with the ACE-2 pathway, it will also be important to determine and another pathway for the penetration of coronavirus into the cell in children through a molecule, the cluster of protein differentiation (CD147) [also called extracellular matrix metalloproteinase inducers (EMMPRIN) or Basigin (BSG). In Endothelial Dysfunction in (IC) CHAOS, virus-caused infected, becomes relevant the role of metalloproteinase ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), zinc-containing enzyme that cleaves von Willebrand factor (vWf), a large protein involved in blood clotting. In thrombophilia with thrombosis, the substances of extracellular traps of neutrophils (Neutrophil Extracellular

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Traps, NETs) are important, which conducive to the development of veno-arterial thrombosis (immune thrombosis), incl. atherosclerosis [27].

Oxidative and Nitro-Galogenic Stress in patients with SARS-Cov2/COVID/19 modify the ratio of cholesterol / phospholipids in dyslipidemia in cell membranes and determines the fluidity or rigidity of the cell membrane.

Phospholipids and cholesterol are part of the lipoproteins of cell membranes and cellular organelles, which in membranes can also be in a free, non-protein-bound state. The ratio of cholesterol / phospholipids determines the fluidity or rigidity of the cell membrane, which is indicate by the increased rigidity of cell membranes during less deformed red blood cells patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), in this case, as a complication of coronavirus infection COVID-19. The ratio of cholesterol/phospholipids in the composition of bile predetermines the degree of bile lithogenicity, of tendency to form of cholesterol gallstones. The ratio of cholesterol / phospholipids in the composition of plasma lipoproteins, along with the molecular weight of lipoproteins (HDL, LDL or VLDL), determines the degree of cholesterol solubility and its atherogenic properties.

Metabolism the life support of the cell is carried out by equilibrium by oxidizing (oxidant) and reducing (antioxidant) systems. When running Oxidative and Nitro-Galogenic Stress in patients with SARS-Cov2/COVID/19, one of the aggressive molecule ROS are hydroxyl radicals, and for RNS peroxynitrite ONOO−. These are of the most cytotoxic molecules that damage fats, proteins, DNA. Disorder of the cell leads to its necrosis. Increases the content of high-density lipoproteins (HDL) and reduces the ratio of LDL / HDL and total cholesterol / HDL.

Double bonds of polyunsaturated fatty acids make cell membranes vulnerable to ROS and RNS damage, causing peroxidation. Fluidity, permeability, signal transmission is disturbed in the cell, receptors, mitochondrial DNA and nuclei are changed. There is a disorder in the regulation of cell membrane renewal and their permeability, as well as the synthesis of prostaglandins - immune defense regulators, leukotrienes and other biologically active substances. During oxidation, aggressive ROS and RNS appear and accumulate in mitochondria.

The universal model of cell life support is plant photosynthesis, producing oxygen, the concentration of Reactive Oxygen Species becomes very high, but the cell lives thanks to the antioxidant system restorers balance.

Thrombus formation in COVID resembles the Antiphospholipid Syndrome.

Thrombus formation in COVID resembles the Antiphospholipid Syndrome, in which antiphospholipid antibodies destroy endothelial phospholipids, provoke AVDS with imbalance in the coagulation / anticoagulation systems with the formation of arteriovenous thrombi on the background of thrombocytopenia. Phospholipids are an important structural component of cell membranes, supporting the cell framework, are involved in the processes of physico-biochemical molecular transport, enzymatic, the damage of which leads to disorders of the cell membranes of the vascular endothelium with the development of thrombi.

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The Hydrogen antioxidant activates the anti coronavirus effect lipid therapy against the background of dyslipidemia disorders.

Given the successful treatment of SARS-Cov2/COVID/19 patients [28] and further scientific research on using Intralipid in SARS-Cov2/COVID/19 [29-32] patients made it possible to notice the absence or development of minor fibrotic pulmonary. The use of Intralipid in the early stages also made it possible to describe the antiviral effect of anti-SARS-Cov2/COVID/19, Intralipid blocks the entry of the SARS-Cov2/COVID/19 virus into cells by maintaining receptor a leucine-rich repeat containing 15(LRRC15), an angiotensin-converting enzyme 2 receptor competitor. [33,34]. Described disrupting the opening / closing of the Mitochondrial permeability transition pore-dependent Ca^{2+} uniporter, mPT pore [29,35]. Coinciding with destruction of lipid rafts that stops the movement of Ca^{2+} waves in cells and calcium ion surges modify functions of normal and pathologically altered cells, such as proliferation, maintenance of life, apoptosis and necrosis. When prescribing lipid-lowering, Statins, Simvastatin, which Downregulates the SARS-CoV-2-Induced Inflammatory Response and Impairs Viral Infection Through Disruption of Lipid Rafts. [36,37]. IPB02V3 and IPB24 lipopeptides displayed greatly increased potencies against the infection of authentic Omicron strain relative to the WT virus [38].

Phospholipids in cell bilipid layer membranes, explain the multisystem nature of the SARS-Cov2/COVID/19 inflammatory lesion of the whole organism on the one hand, and how lipid therapy for the correction of dyslipidemia, lipid peroxidation with proven and antiviral effects of lipids. Scientists drew attention to the cytoprotective and cytodestructive significance of lipids.

Based on the fundamental sciences of chemistry, biology and biochemistry of membrane lipids, the mechanisms of protection and cell damage are universal. Depending on the disorders of the element's hydrogen, carbon and oxygen atoms, as well as phosphorus, sulfur, nitrogen and other elements that determine cellular function. Disorder of oxygen and nitrogen in the form of Oxidative and Nitro-Galogenic Stress in Patients with SARS-Cov2 / COVID / 19 when generating Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) is described [29], phosphorus, as ATP energy carrier [35,39]. Now examine the role of hydrogen. Japanese doctor Tazawa Kenji, Professor of Medical and Pharmaceutical University Toyama, author of scientific articles on hydrogen therapy described the effect of molecular hydrogen as an antioxidant. Hydrogen at permissive pH - penetrates bio membranes and suppresses ROS in mitochondria, in the nucleus where they damage DNA, and it is the only antioxidant that easily crosses the blood-brain barrier and has an antioxidant effect in the central nervous system, helping to deliver beneficial substances to all cells of our body, normalizing metabolism. Hydrogen prevents lipid metabolism disorders, dyslipidemia, reduces the amount of visceral fat, lowers high cholesterol levels and increases the body's sensitivity to cholesterol. Raises the tone of the organism. Restores immune defense to normal. Effectively protects against cancer. Suspends the aging process. Restores metabolism. Removes toxins. Thus, hydrogen is the best antioxidant that does not give side effects and has no contraindications. For these purposes, Hydrogen Enriched Water (HEW)/Hydrogen Water, which is simply water enriched with molecular hydrogen, in which hydrogen gas molecules H2 are dissolved [40], has proven itself well. Tyler LeBaron, founder of the Molecular Hydrogen Institute, considers the anti- SARS-Cov2 / COVID / 19 effect of H2 by activating and regulating the Nrf2 system, which maintains homeostasis, regulates inflammation, reduces chronic systemic inflammation, and selectively reduces hydroxyl ion (OH-) and Peroxynitrite (ONOO-), reducing cytokine storm, regulates the production of enzymes, and not just reduces or inhibits them. The transcription factor NRF2 is a basic leucine (in the composition

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of the leucine receptor is a rich repeat containing 15 (LRRC15) responsible for blocking the entry of the SARS-Cov2/COVID/19 virus into cells) zipper protein (bZIP) that can regulate the expression of antioxidant proteins that protect against oxidative damage. By preserving the normal metabolism of redox reactions, the use of hydrogen counteracts the reactive inflammatory response associated with the cytokine storm. It has antioxidant, anti-inflammatory, hormone-regulating and anti-apoptotic properties. Stimulates the outflow of sputum, improves the saturation of the lungs and reduces the risk of severe development of the disease. Hydrogen modifies the cascades of lipid peroxidation, protein phosphorylation, and gene expression, resulting in anti-inflammatory, anti-allergic, and potential anti-aging properties [41].

Hydrogen Enriched Water (HEW)/Hydrogen Water not to be confused with deuterium D/²H, "heavy water" which inhibits some cleavage reactions.

Hydrogen Enriched Water (HEW)/Hydrogen Water not to be confused with deuterium D/²H, "heavy water" which inhibits some cleavage reactions. The removal deuterium D/²H, "heavy water" is possible due to the effect of compression and reduction of "synairesis" of proteins, separation of liquid from the gel caused by a reduction in protein due to the release of water from the membrane and the release from cell membranes and cells, by Multiple Organ Support Therapy, MODS, in context Extracorporeal Life Support Organization & Extracorporeal oxygenation ECMO; Extracorporeal methods of detoxification (Plasmapheresis) and biocryoperfusion [13,14].

Conclusions

Lipid therapy for dyslipidemia disorders activates the antioxidant Hydrogen, with anti-coronavirus effect which at permissive pH restores its destruction, in the body infected with this virus. In combination Multiple Organ Support Therapy, MODS, in context Extracorporeal Life Support Organization & Extracorporeal oxygenation ECMO; Extracorporeal methods of detoxification (Plasmapheresis, etc.); Microcirculatory-Mitochondrial Recruitment Microcirculatory-Mitochondrial Distress Syndrome. Which lead to by eliminating hypo(an)ergic mitochondria carried out by lysosomal clearance (mitophagy), thus demonstrating eu-ergic mitochondria with normalization the transition of the mitochondrial permeability pores and the uniporter-Ca++ channel, supported by the Universal Hydrogen Antioxidant which productively restores oxidizable biological substrates destroyed by the toxic Reactive Oxygen Species and reactive nitrogen species [42]. As LeBaron notes, the Nrf2 system, which is involved in phase 2 of ROS detoxification, regulates more than 200 protective proteins and enzymes in the body, the Nrf2 system is depleted and can no longer regulate inflammatory processes.

Accordingly, more mechanistic and clinical studies of this new medical gas are needed to combat the complications of COVID-19. What we have seen and described already after the application of Intralipid [29], which interacts with hydrogen and possibly improves the Nrf2 depleted antioxidant system.

In the direction of successful treatment of critical conditions, we have been actively working since 1984, published to anaphylactic shock [43], exfusion of lymph in exotoxic shock [44], the recovery of patients from coma [45], 40 years of maternal absence of mortality on the operating table [39], extracorporeal bioperfusion and cryobioperfusion to reduce deuterium D/²H, "heavy water" from cell membranes, from the cell, nucleolus, DNA [46-48] and many, many others.

Since failure to treat SARS-Cov2/COVID/19 may result in Chronic Obstructive Pulmonary Disease [49] or the need for a lung transplant [50].

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Glad I was on the right track. Transgenic pig as a donor carrier of an immunosyngenic xenoorgans for organ transplantation to a recipient human. At one time (1984) i proposed an immuno sigenic transgenic pig as a carrier of donor organs for transplantation to a recipient. The scientific path for 40 years, successfully solved by US scientists [51], for which I sincerely thank them.

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