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Patho-physiology of later-stage complications of COVID-19 similar to poisoning effects of arsenic and mercury – from the perspective of homoeopathy

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Abstract
Life-threatening complications in later-stage of COVID-19 are found especially in patients who have different co-morbidities. Various recently published researches and reviews explain that dysregulated host defensive mechanisms with vascular endothelial disorders related to reduction of nitric oxide (NO) are responsible for these complications. On the other side, different researches reveal the poisoning effects of Arsenic as well as Mercury have the similar types of pathophysiological activities. These poisoning pathologies can identify the deranging capability of these substances.

Keywords: Endothelium, cytokines, nitric oxide, arsenic, mercury

Introduction
COVID-19 is primarily considered as a disease of respiratory system caused by SARS-CoV-2. Among the infected patients, majority of them fight it off effectively with having few or no symptom. Typical immune response is sufficient enough to overcome it. But the small portion of them unable to do so and tragically succumb because of dysregulated host response leads to life-threatening organ dysfunction. The factors which are primarily thought to be responsible are lymphopenia, high level of pro-inflammatory cytokines, hyper-coagulability, hypertension, diabetes, age, being male etc. All these factors are directly or indirectly related to the later complications represented as endothelial disorders with a background of decreased endothelial NO production or it's bioavailability [1-4].
On the other hand, inorganic substances Arsenic as well as Mercury exposure increases pro-inflammatory cytokines production and causes reduction of lymphocytes, thrombosis formation, endothelial disorders with impaired NO production and complications related to different co-morbidities like hypertension, diabetes, being aged, being male etc [1, 5-25].
According to homoeopathic concept, the poisoning effects can reveal the hidden capability of that drug to derange in the similar manner which can be related to the curative virtue in homoeopathic preparation in suitable form [26-28].

Later-stage complications of covid-19
Endothelial Disorders
Vascular endothelium is a monolayer of cells, lying on the vascular smooth muscle cells. Besides their function as cellular barrier, the endothelial cells provide crucial interface between blood compartment and tissues, and play an important role in host defence by initiating and governing the initial steps of the immune response. While, epithelial cells are related with initial sensors of danger, the vascular endothelium acts as the portal governing the entry of leucocytes in to the effected tissues to fight against the invaders followed by repairmen and heal the wound. This coordinated host defence mechanisms can also contribute to disease when the usual homeostatic and defensive functions over-reach and turn against the host. In this respect, the innate and adaptive immunity depends on a series of leucocyte adhesion molecules which expressed at negligible levels under physiological circumstances. The elevated expression of the endothelial-leucocyte adhesion molecules depends on irritative stimuli, principally because of pro-inflammatory cytokines. By this way, the pro-inflammatory cytokines, such as interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) in excess contribute to a pathological process from its normal defensive orchestrated protective function.

In large number of productions of these activated pro-inflammatory cytokines cause the condition termed as "cytokine storm". Under these circumstances the inflammatory activation of endothelial cells can disrupt vascular endothelial cadherine and express matrix metalloproteinases leads to degradation of the basement membrane and interrupt endothelial barrier function. In lung tissues the impairment of this barrier function leads to protein accumulation in the alveolar space, resulting accumulation of fluid which impairs oxygenation of the blood. Impair barrier function also leads to capillary leak, which aggravate acute respiratory distress syndrome. [3, 29-31]

In addition to that, in the hepatocytes, IL-6 also acts as a principal regulator of production of fibrinogen - the precursor of clots, plasminogen activator inhibitor-1 - a major inhibitor of endogenous fibrinolytic mediators and C-reactive protein - a bio-marker of these acute inflammatory phenomena[32,33]. Cytokine storm also provoke a prothrombotic and antifibrinolytic imbalance which cause thrombin accumulation, and beyond the pulmonary parenchyma this predisposition exists in peripheral vein and arteries from brain to distal lower extremities, within microvasculature of coronary circulation, in the kidneys etc. So, disordered endothelial homeostasis influenced by pro-inflammatory cytokine storm provides a common thread in numerous complications of COVID-19 [34-36].

Role of endothelial NO

NO is a soluble gas synthesized in vascular endothelium from the amino acid L-arginine in a reaction catalyzed by the endothelial enzyme Nitric Oxide Synthase (NOS). It has wide range of biological properties to maintain vascular homeostasis and normal endothelial function by regulating vascular tone, local cell growth, protection from injuries consequences of platelets and cells circulating in blood etc. by its antioxidant, anti-inflammatory and anti thrombotic activities[37]. In COVID-19 patients NO levels are found to be significantly lower and this low level of NO has close relation with vascular dysfunction and immune inflammation [74, 38, 39].

It has been described that Angiotensin-converting enzyme 2 (ACE2) acts as SARS-CoV-2 receptor regulates the vascular function by modulating NO release and oxidative stress [38, 40-42]. SARS-CoV-2 invades host cells through its surface stimulating glycoprotein-S protein binding to ACE2, and then down-regulates the expression of ACE2 [42].

On the other side, ACE converts angiotensin I (AngI) into Angiotensin II (AngII). This AngII is proinflammatory. But, ACE2 degrades this pro-inflammatory AngII to Angiotensin (1-7) (Ang-(1-7)). This Ang-(1-7) promotes endothelial cells to produce NO. As a result of down-regulation of ACE2, ACE inhibits NO production and promotes reactive oxygen species (ROS) production and inflammation. Not only that, pro-inflammatory peptide AngII activates macrophages to produce pro-inflammatory cytokines and ROS, results excessive inflammatory response and NO/ROS imbalance, leads to oxidative stress [43-45].

So, a strong and persistent cytokine storm resulting significant increase of pro-inflammatory cytokines and chemokines leads to high inflammation and severe imbalance of NO/ROS. This leads to oxidative stress cause damage to multiple tissues and organs. Pro-inflammatory cytokines promote production of excess ROS in the mitochondria by blocking mitochondrial phosphorylation and adenosine triphosphate production[2]. Excess ROS aggravates endothelial injury through growth and migration of vascular smooth muscle and inflammatory cells, cell apoptosis, activation of transcription factors (Nuclear factor kappa B, Activator Protein-1) and over expression of inflammatory cytokines and adhesion molecules (Intercellular adhesion molecule-1, Vascular cell adhesion molecule-1, E-selectin) [46]. It also causes reduction of NO production[47]. Reduced production and/ bioavailability of endothelial NO leads to disturbances of host defensive potential mechanisms from its normal vasodilatation, antithrombotic, anti-inflammatory and antiviral as well as antibacterial properties [48].

It has been reported that, the important co-morbidities of COVID-19 like, hypertension, diabetes, and cardiovascular diseases found to be associated with vascular dysfunction and decreased endothelial NO production or it's bioavailability. Other than the hypertensive and hyperglycaemic patients, pre-existing endothelial dysfunction related to decrease NO production is also found in the elderly, and the patients with low levels of vitamin D [38].

So, increased level of endothelial NO availability is directly related to the antiviral resistance against this COVID-19 pandemic and this decrease endothelial NO production or bioavailability strongly associated with COVID-19 mortality can open an alternative therapeutic and preventive target as well [39].

In this consequence, the sexual hormone oestrogen causes increase expression and activity of endothelial NOS resulting higher NO production in the systemic vasculature of female [49]. Androgens, particularly testosterone is suspected to play a critical role to increase the risk[50]. In one side, influence of testosterone enhances the expression of key cellular receptors (i.e., ACE2) that allow viral entry and fusion, and in other side, it has been found to suppress pro-inflammatory cytokines IL-6, TNF-α activity and enhance the anti-inflammatory response. So, hypogonadism is related to dangerous overactive immune response [51].

Poisoning effects of arsenic & mercury

Later-stage complications of COVID-19 are related to up-regulated pro-inflammatory cytokines in the form of cytokine storm and reduction of lymphocytes, impaired NO with endothelial disorders, intravascular thrombosis, existing co-morbidities, activity of oestrogen and testosterone determine the genders susceptibility. All these phenomena have been similarly found in the poisoning effects of both of these inorganic substances, which are following –

Arsenic Poisoning

1. **Up-regulated pro-inflammatory cytokines and Reduction of Lymphocytes:** Arsenic exposure changes the levels of pro-inflammatory cytokines. It can increase TNF-α and IL-1, IL-2, IL-6, IL-8 significantly [5-8].

   Functionality of Lymphocytes can be reduced by the Arsenic which leads to suppression of immune system. Arsenic exposure causes impaired regulatory T-Cell functions [5, 7, 9].
2. **Thrombosis formation:** Arsenic enhances platelet aggregation and has capability to reduce fibrinolysis cause arterial thrombosis leads to cardiovascular

disorders [10-12].

3. **Endothelial disorders with impaired NO production or it's bioavailability:** Exposure of Arsenic causes impairment of NO formation in the vascular endothelium and high oxidative stress is resulting endothelial dysfunctions. It induces atherosclerosis by increasing the platelet aggregation and reducing fibrinolysis [11, 12].
4. **Related to co-morbidities:** Different epidemiological studies in Arsenic-endemic areas have found a positive relationship between Arsenic exposure and hypertension. In experiments it has been indicated that hypertension developed through promotion of inflammation, oxidative stress and endothelial dysfunction [13]. Arsenic exposure also enhances the risk of diabetes and obesity. Inflammation, oxidative stress and apoptosis contribute to the pathogenesis of Arsenic-induced diabetes and obesity [14, 15]. Upregulated cytokines caused by Arsenic poisoning are well-known for their action on insulin resistance and beta cell dysfunction [8].
5. **Gender susceptibility:** Males are more susceptible to chronic Arsenic poisoning than female[16]. In another study it has been found that child bearing age may be due to influence of sex hormones, women have higher detoxifying efficiency than men in a highly arsenic exposed population [17].

Mercury Poisoning

1. **Up-regulated pro-inflammatory cytokines & Reduction of Lymphocytes:** Exposure of Mercury detected higher concentration of pro-inflammatory cytokines IL-1 β, IL-6, IL-8, TNF- α and Interferon-γ [1, 18]. Early inflammatory response with activation of IL-6 and IL-8 expression is found in the pathogenesis of Methyl Mercury [19].
   Expression of decreased T- Lymphocyte is a contribution of immune-toxic effect of inorganic Mercury [20].
2. **Thrombosis formation:** Mercury increases platelet aggregation and thrombosis induced coagulation by increasing factor VIII, platelet factor-4, thrombin and protein C [21]. Mercury may cause procoagulant activity in erythrocytes, leading to thrombosis [22].
3. **Endothelial disorders with impaired NO production or bioavailability:** Vascular effects of Mercury increase oxidative stress and inflammation, reduced oxidative defence, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia[21]. Mercury suppresses NO synthesis and activates proinflammatory cytokine expression [23].
4. **Related to co-morbidities:** Mercury decreases NO bioavailability. Clinically hypertension, coronary heart disease, myocardial infarction, cardiac arrhythmias, reduced heart rate variability, increased carotid intima-media thickness and carotid artery obstruction, cerebrovascular accident, generalised atherosclerosis, and renal dysfunction are found in this poisoning [21]. Diabetes and obesity are common co-morbidities of COVID-19. Mercury has a demonstrated link with these. Not only that, Selenium deficiency is found to be associated with COVID-19 death and mercury can deplete this selenium [1].
5. **Gender susceptibility:** Testosterone potentates mercury toxicity, oestrogen is protective [24]. Similarly, boys are found to be more susceptible to neurotoxic effects of methylmercury [25].

Importance of poisoning in homoeopathic pathogeneses

Homoeopathic drug pathogeneses are collected from three basic sources - drug proving, clinical observations and poisoning effects of the drug substance. Homoeopathic proving cannot be extended beyond the level of functional changes. The clinical observations need time and verifications through treatment. In this respect, when there is an advance state of a new disease and lack of opportunity to treat it, the existing known poisoning phenomena of any drug substances in the form of their capability to produce similar type of pathological complications bear important value. In aphorism no.110 of Organon of Medicine, Samuel Hahnemann recommends the poisoning effects of different drug substances as the curative power to the similar type of suffering in nature[26]. According to Richard Hughes, the poisoning virtue of the drug substances aids us greatly in arriving at the lessons the drugs can produce and in obtaining similarity of seat between drug action and disease, thus records of poisoning and works on toxicology have therefore been always largely employed, from Hahnemann downwards, in the construction of pathogeneses [27]. W.M. Boericke says records of poisoning give the ultimate action, the tissue and organic changes that the provings can only indicate, and thus they illustrate and interpret the provings[28]. So, the poisoning effects can reveal the hidden capability to derange in the similar manner and this pathogenetic virtue can be related to the curative power of that particular drug substance to the similar type of suffering.

Conclusion

Later-stage complications of COVID-19 are related to different co-morbidities, like hypertension, diabetes, being aged etc. Dysregulated host defence mechanisms, when the usual homeostasis and defensive functions over-reach, turn against the host through cytokine storm resulting high inflammation, endothelial disorders with NO/ROS imbalance. All these phenomena are also related to intravascular accumulation of thrombus and this predisposition found beyond the lung in peripheral vascular system. On the other hand, both Arsenic and Mercury poisoning have similar type of patho-physiological changes as seen in later-stage complications of COVID-19. In homoeopathy, disease producing power is being considered as a capability to cure the same. So, similar patho-physiological changes to the later-stage complications of COVID-19 found in the poisoning of Arsenic and Mercury, indicate their capability to fight against the same if use in homoeopathic dilution.

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