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BRIEF NOTE

The potential role of physical activity and a healthy diet in increasing nitric oxide during COVID-19 outbreak

Les rôles potentiels de l'activité physique et d'une alimentation saine dans l'augmentation de l'oxyde nitrique pendant l'épidémie de COVID-19

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Summary The potential role of physical activity and a healthy diet in increasing nitric oxide during COVID-19 outbreak. This manuscript presents a perspective which provide new insights about the promising role of nitric oxide on COVID-19. Demonstration that nitric oxide was an important cornerstone against viral infections, including SARS-CoV-1 in 2009. Thus, given the concern that higher NO^- could improve endothelial health and might be a protection factor against COVID-19, should we critically consider non-pharmacological strategies that increase NO^- bioavailability as medicine for COVID-19? From this perspective, we highlight the potential effect of physical activity and healthy diet in stimulating the increase of NO^- bioavailability.

MOTS CLÉS
COVID-19 ;
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Activité physique ;
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Exercice physique ;
Pandémie

Résumé Les rôles potentiels de l'activité physique et d'une alimentation saine dans l'augmentation de l'oxyde nitrique pendant l'épidémie de COVID-19. Ce manuscrit présente une perspective qui fournit de nouvelles informations sur le rôle prometteur de l'oxyde nitrique sur la protection contre le risque de COVID-19. Dès 2009, a été évoqué le rôle de l'oxyde nitrique contre le risque d'infections virales, y compris contre la première pandémie liée au coronavirus SARS-CoV-1. Compte tenu de l'hypothèse qu'une augmentation de la production de NO^- permettrait d'améliorer la santé endothéliale et pourrait être un facteur de protection contre COVID-19, la question se pose sur la promotion de stratégies non pharmacologiques

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qui augmentent la biodisponibilité du NO^-. C'est dans cette perspective que sont, ici, discutés les effets potentiels de l'activité physique et d'une alimentation saine pour stimuler l'augmentation de la biodisponibilité du NO et la prévention contre la COVID-19.

1. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and chronic diseases

The strong virulence and spread of SARS-CoV-2 resulted in the coronavirus disease 2019 (COVID-19) pandemic with number of infected and dead people still increasing over the planet. At this point, thousands of people are infected and fighting somehow against this invisible enemy. The deadly impact of this virus has created an environment of fear and uncertainty, especially for, but not exclusive to, people with chronic diseases who have been the mostly affected by disease [1]. Endothelial dysfunction and consequent decrease in nitric oxide (NO^-) levels may be a key factor in accelerating the progress of SARS-CoV-2 infection leading to the highest severity of COVID-19 disease in those already chronically ill [2].

It is known that the endogenous production of NO^- is involved in the protection against several vascular and cardiac diseases [3]. Moreover, in 2004, a study demonstrated that low-dose inhaled NO^- could shorten the time of ventilatory support in patients infected with SARS-CoV-1 [4]. Although the effect of NO^- on SARS is still unknown, this molecule can be truly relevant in the prevention and treatment of the comorbidities associated to COVID-19.

2. Nitric oxide role in the prevention and treatment of COVID-19, can the past and the present be allies?

Endogenously, the NO^- is synthesized by a family of three isoforms of nitric oxide synthases (NOS): neuronal (nNOS), endothelial (eNOS) and inducible (iNOS) [3,5]. All of them require of L-arginine and molecular oxygen followed by a sum of cofactors to produce NO^-. When produced, this gaseous signaling molecule play a key role in the regulation of numerous pathways (Fig. 1) related to the treatment of different diseases [3].

We highlight that NO^- can be a biosynthetic factor for the building of natural products with a nitrogen-nitrogen bond as 1,2,3-triazolopyrimidine scaffold of 8-azaguanine, which set forth a vast range of antimicrobial, anti-inflammatory and antiviral activities [6]. Furthermore, when NO^- reacts with molecular oxygen, it became a more nitrosative substance capable to interact with the nucleophilic sulfur of the thiol (SH) group of cysteines by the S-nitrosylation process [7]. Thus, viral cysteines-containing enzymes can be nitrosylated by NO^- products [8].

Considering that several viral-encoded proteins present reactive cysteine, NO^- can impair the virus development in the host. In this regard, NO^- antiviral role was already demonstrated among different families of DNA and RNA of virus, including *Coronaviridae* [8]. In 2009 [9], it was found that NO^- inhibits the replication of SARS-CoV-1 mainly by the reduction of the spike protein palmitoylation, affecting the interaction between this protein with its respective receptor: the angiotensin converting enzyme 2. They also verified that NO^- causes a reduction in viral RNA production at the beginning of viral replication. Although this finding was in SARS-CoV-1, it should be partially generalized to COVID-19 since they present genetic similarities [10].

On the other hand, caution is needed when interpreting the role of NO^-. When lipopolysaccharides stimulation occurs in neutrophils and macrophages, increases the iNOS-derived NO^-, which is one of the one of the main agents for inducing sepsis [11]. Moreover, NO^- interacts with NADP(H) oxidase generating peroxynitrite leading to a immunosuppression [11]. In this regard, it must be important to note that the beneficial effect of NO^- may depend of the eNOS and nNOS expression [12].

The eNOS and nNOS-derived NO^- may act as an antagonist of the effects of SARS-CoV-2 [2] due to its selective pulmonary vasodilatation, lowering pulmonary vascular resistance, pulmonary hypertension, edema formation and, consequently, risk of thrombosis [13,14]. Also, due to NO^- anti-inflammatory properties, it can also reduce the production of pro-inflammatory protein by vascular regulation [4,13]. Therefore, NO^- might improve arterial oxygenation being a potential treatment for COVID-19, which was historically used as a treatment of SARS-CoV-1.

According to the historically role of NO^-, it was an important cornerstone against viral infections, including SARS-CoV-1. Thus, given the concern that higher NO^- could improve endothelial health and might be a protection factor against COVID-19, should we critically consider non-pharmacological strategies that increase NO^- bioavailability as medicine for COVID-19? From this perspective, we highlight the potential effect of physical activity and a healthy diet in increasing NO^- bioavailability.

3. Exercise-induced NO^- and NO^- rich-diet as medicine against COVID-19

It has already being speculated that physical activity might induce protective effects against SARS-CoV-2 from a plethora of signaling in cardiorespiratory, musculoskeletal and nervous system [15]. However, we are opening a perspective that NO^- may be a key that triggers the exercise-related benefits, which is also applied for healthy diet against SARS-CoV-2. Here, we will explain how nitric oxide can be boosted by exercise and nutrition.

During exercise-training, the fluids of the organism starts to flow faster to better transport oxygen and nutrients to

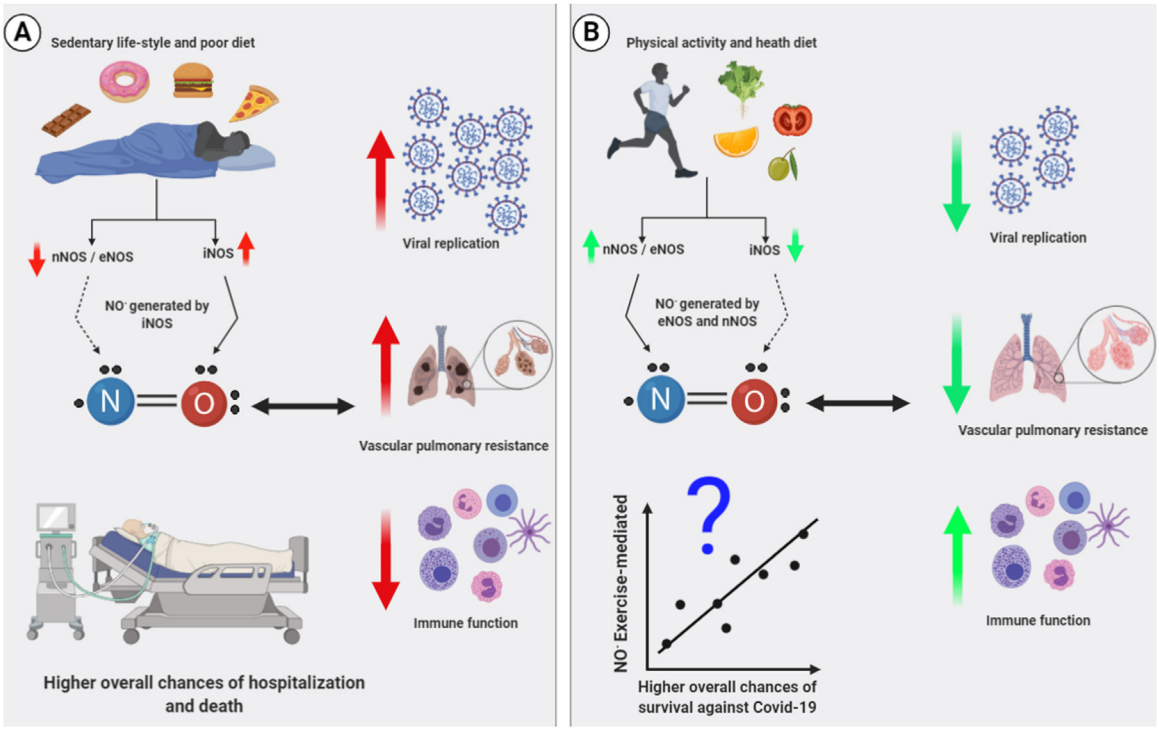

Figure 1 The possible pathways of physical activity and healthy diet-derived NO^- in case of SARS-CoV-2 infection. A. For a sedentary lifestyle with a poor diet, NO^- will be generated, predominantly, by iNOS which will increase inflammation and oxidative stress leading to an increase in viral replication, vascular pulmonary resistance, and, consequently, immunosuppression. These conditions can lead to a worsened prognosis in SARS-CoV-2 infection, which may increase the overall risk of hospitalization and death. B. Physical activity concomitant with a healthy diet can lead to an increase in NO^--eNOS derived, which has anti-inflammatory, antioxidant, and anti-viral properties, possibly acting as a protector factor against viral replication, vascular pulmonary resistance, and immunosuppression. However, the hypothesis to test is whether higher physical activity and healthy diet-derived NO^- increase the overall chances of survival against COVID-19.

the muscle tissue. This way, the friction forces between fuids and arterial wall are called shear stress [16,17]. The increase in shear stress will induce a higher expression of eNOS, increasing the generation of NO^- that, in turn, will decrease the concentration of calcium at the smooth muscle cell, leading to vasodilation. Also, shear stress can induce an increase in the activation of superoxide dismutase, which transforms superoxide anion in hydrogen peroxide; in turn, it will lead to a feedback loop to express eNOS. Regardless of shear stress, NO^- bioavailability can also be increased by vasoactive peptides and proteins induced by muscle contraction [16]. This way, it is common to find several reports of exercise-trained individuals, mainly older ones, with higher basal levels of NO^- [18]. Furthermore, in healthy people, NO^- seems to be intensity-dependent since higher intensities exercises promotes a more substantial increase in NO^- in relation to lower intensities [19]. However, to work in higher intensities requires a better dose-response control to not provoke an immunosuppression by over-reaching or over-training [18,20].

Although we constantly produce endogenous NO^- through L-arginine-NOS pathway, there are other sources to generate NO^- such as the nitrate-nitrite-NO^- pathway, which can be stimulated by the ingestion of a high concentration of nitrate diet (e.g. lettuce, spinach and beetroot) [21]. This kind of diet significantly increases the bioavailability of NO^-, and it has already been reported that it promotes beneficial effects on insulin resistance, chronic obstructive pulmonary disease, cancer, and osteoporosis [21]. Hence, an important hypothesis to test is whether exercise-training depends on the NO^- bioavailability to be a protection factor to the COVID-19, as well as the impact of high-NO^- against SARS-CoV-2. Although the present study presented several pathways related to NO^- acting as a protective mechanism for the SARS-CoV-2, there still a lack of consensus in relation to the real involvement of NO^- in this specific virus. Therefore, the hypothesis of the present study should be interpreted with caution since the type of the NOS isoform and the clinical condition of the patient should also be considered.

It is recommended that future clinical trials report and discuss any impact of NO^- on SARS-CoV-2 infection, such as the effect of NO^- derived from exercise training and healthy diet on respiratory infections. This could improve our understanding with respect to the safety and clinical applications of proper exercise and strategic nutrition as prevention, treatment, and rehabilitation. Such information is important to help assess whether the long-term benefits of those behavioral factors can impact on the COVID-19 outbreak as well as other possible viral infections.

Disclosure of interest

The authors declare that they have no competing interest.

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