Long COVID: Advances in Diagnosis, Biomarkers, and Innovative Therapies

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ABSTRACT

Introduction: Long COVID is a medical condition that affects individuals who have had COVID-19 and whose symptoms persist beyond three months after the acute phase. The World Health Organization (WHO) defines it as a multisystem syndrome that affects systems such as the respiratory, cardiovascular, neurological, and gastrointestinal systems, and significantly affects quality of life. The most common symptoms include extreme fatigue, shortness of breath, cognitive disorders, sleep disturbances, and muscle pain.

State of the art: Although the exact mechanisms are not fully understood, several possible causes have been identified, such as viral persistence, chronic inflammation, and mitochondrial dysfunction. Immune imbalance is a central factor, as an exacerbated immune system response generates a persistent inflammatory state. Overproduction of cytokines, such as interleukin-6 (IL-6), along with autoimmune processes, contribute to prolonged tissue damage. Furthermore, patients with comorbidities, a history of severe illness, or lack of vaccination are at higher risk of developing Long COVID. The microbiota also plays a relevant role. Its alteration (dysbiosis) could amplify systemic inflammation and neurological symptoms. Recent research explores microbiota modulation through probiotics as a possible therapeutic strategy. However, clinical studies are in their initial stages. In parallel, some antivirals and immunomodulators are being evaluated, although there is still no standardized treatment. Despite these limitations, vaccination has proven effective in reducing the incidence of Long-COVID, as well as the severity of its manifestations. Currently, multiple international studies seek to identify risk factors, diagnostic biomarkers, and new therapeutic options.

Discussion : Long-COVID represents a major health challenge that requires coordinated responses.

Conclusion: A review of the pathogenetic mechanisms, immunological implications, and potential therapeutic strategies highlights the need for a multidisciplinary approach that integrates basic, clinical, and epidemiological research. Only through this approach will it be possible to move toward more accurate diagnoses and effective treatments that improve the quality of life of affected patients.

Keywords: Long-COVID, SARS-CoV-2, inflammation, dysbiosis, vaccination, antivirals, biomarkers, neurological sequelae.

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COVID persistente: Avances en el diagnóstico, biomarcadores y terapias innovadoras

RESUMEN

Introducción: el COVID persistente es una condición médica que afecta a individuos que han padecido COVID-19, cuyos síntomas perduran más allá de tres meses posteriores al cuadro agudo. La Organización Mundial de la Salud (OMS) lo define como un síndrome multisistémico que compromete aparatos como el respiratorio, cardiovascular, neurológico y gastrointestinal, y afecta considerablemente la calidad de vida. Entre los síntomas más comunes se incluyen fatiga extrema, dificultad para respirar, trastornos cognitivos, alteraciones del sueño y dolor muscular.

Estado del arte: aunque los mecanismos exactos no están completamente esclarecidos, se han identificado varias posibles causas, como la persistencia viral, la inflamación crónica y la disfunción mitocondrial. El desequilibrio inmunológico constituye un factor central, ya que una respuesta exacerbada del sistema inmunitario genera un estado inflamatorio persistente. La sobreproducción de citocinas, como la interleucina-6 (IL-6), junto con procesos autoinmunes, contribuye al daño tisular prolongado. Asimismo, los pacientes con comorbilidades, antecedentes de enfermedad grave, o falta de vacunación presentan mayor riesgo de desarrollar COVID persistente.

La microbiota también desempeña un papel relevante. Su alteración (disbiosis) podría amplificar la inflamación sistémica y los síntomas neurológicos. Varias investigaciones recientes exploran la modulación de la microbiota a través de probióticos, como posible estrategia terapéutica. No obstante, los estudios clínicos se encuentran en fases iniciales. De manera paralela, algunos antivirales e inmunomoduladores están siendo evaluados, aunque aún no existe un tratamiento estandarizado. Pese a estas limitaciones, la vacunación se ha mostrado eficaz en reducir tanto la incidencia de COVID persistente, como la gravedad de sus manifestaciones. Actualmente, múltiples estudios internacionales buscan identificar factores de riesgo, biomarcadores diagnósticos y nuevas opciones terapéuticas.

Discusión: el COVID persistente representa un desafío sanitario de gran magnitud que exige respuestas coordinadas.

Conclusión: la revisión de los mecanismos patogénicos, la implicación inmunológica y las posibles estrategias terapéuticas ponen de relieve la necesidad de un abordaje multidisciplinario que integre investigación básica, clínica y epidemiológica. Solo mediante este enfoque será posible avanzar hacia diagnósticos más precisos y tratamientos eficaces que mejoren la calidad de vida de los pacientes afectados.

Palabras clave: COVID persistente, SARS-CoV-2, inflamación, disbiosis, vacunación, antivirales, biomarcadores, secuelas neurológicas.

INTRODUCTION

The World Health Organization (WHO) defines long COVID as a "post-COVID-19 condition" when symptoms persist for more than three months after infection, in the absence of an alternative diagnosis. This condition affects multiple organ systems, particularly the pulmonary system.[1,2]

Common symptoms include shortness of breath, fatigue, cognitive impairment ("brain fog"), anosmia, hair loss, sexual dysfunction, and sleep disturbances.[3]

Factors such as severe COVID-19 illness, preexisting conditions, lack of vaccination, repeated infections, sex, smoking status, and age increase the risk of developing long COVID.[1-3]

Infection with different variants of SARS-CoV-2 has been associated with distinct pathological phenotypes. Compared with the original strain and the Delta variant, the Omicron variant is associated with a lower risk.[3]

The aim of this review is to analyze the clinical, immunological, and transcriptomic characteristics of long COVID, as well as the proposed pathogenic mechanisms, risk factors, potential biomarkers, and therapeutic advances. In doing so, this review seeks to provide an up-to-date scientific framework that contributes to a comprehensive understanding of this condition and supports the implementation of a multidisciplinary approach to its diagnosis, prevention, and treatment.

STATE OF THE ART

Pathogenic mechanisms and immune involvement

The pathogenic mechanisms of long COVID include the persistence of the virus or its components within tissues, resulting in chronic inflammation, dysregulated autoimmune responses, mitochondrial and endothelial dysfunction, and microbiota dysbiosis. Reactivation of latent viruses, such as Epstein-Barr virus and varicella-

zoster virus, has also been reported, together with cerebral and neuroendocrine dysfunction and coagulation abnormalities.[3,4] However, the pathogenesis of this condition has not yet been fully elucidated.

With respect to the immunological mechanisms potentially involved, several immune mediators and circulating biomarkers have been described, including cortisol, serotonin, interleukins 8, 4, and 6, macrophage inflammatory protein beta chemokine, and thymic stromal lymphopoietin (IL-8, IL-4, IL-6, CCL4, and TSLP, respectively).[5]

Multiple studies have demonstrated that IL-6 contributes to an inadequate antiviral response, viral persistence, and the long-term inflammation characteristic of long COVID. This cytokine is associated with mannose-binding lectin (MBL), which plays an important role in the neutralization of SARS-CoV-2. Accordingly, low MBL levels may contribute to dysregulated overproduction of IL-6 and to increased disease severity.[5]

Patients with preexisting immune impairment experience difficulties in clearing residual viral reservoirs or infected cells. As a result, viral persistence may contribute to ongoing inflammation and cognitive dysfunction associated with disease progression.[5]

In patients with long COVID, the immune system remains excessively activated, potentially leading to inappropriate immune responses, chronic inflammation, tissue damage, and the development of autoimmune diseases.[6] Autoimmune mechanisms, including excessive formation of neutrophil extracellular traps, have been proposed to play a role. Reported associated autoimmune conditions include Guillain–Barré syndrome, autoimmune encephalitis, Hashimoto's thyroiditis, and vasculitis.[7]

Symptoms

Persistent symptoms of long COVID significantly impair quality of life and include severe fatigue, cognitive impairment, tachycardia, loss of smell and/or taste, insomnia, anxiety, depression, dyspnea, hearing loss, edema, and gastrointestinal disorders. It is crucial that patients receive multidisciplinary medical care to develop individualized treatment plans.[8]

Although cases are more common in adults, recent studies conducted in children and adolescents have shown that approximately 25% presented with more than 40 symptoms attributable to this condition.[9,10] The most frequently reported symptoms included mood disturbances –such as sadness, anxiety, tension, anger, or depression (16.50%)– followed by fatigue (9.66%), sleep disturbances (8.42%), headaches (7.84%), respiratory symptoms (7.62%), nasal congestion (7.53%), and cognitive difficulties, including problems with concentration, confusion, learning difficulties, and memory loss (6.27%).[10,11]

COVID-19 Vaccination

COVID-19 vaccines have been shown to be effective not only in preventing severe infection but also in reducing the risk of long COVID. Several studies conducted in countries such as the United Kingdom, Spain, and Estonia have demonstrated that vaccinated individuals have a lower incidence of prolonged symptoms.[12,13] In Argentina, vaccines such as BBIBP-CorV® (Sinopharm), BNT162b2® (Pfizer), and mRNA-1273® (Moderna) were effective in preventing hospitalizations and persistent symptoms during the Omicron outbreak.[14] Studies from South Korea and the United States further indicate that vaccinated individuals experience symptoms of lower severity and shorter duration.[4,15]

Despite these advances, the underlying mechanisms of long COVID remain complex and multifactorial, and efforts to develop targeted therapies are ongoing.[1] Vaccination continues to be the most effective and accessible intervention to reduce disease burden, consolidating its role as a key strategy not only for preventing acute infection but also for mitigating long-term consequences.

Treatment

Vaccination reduces the risk of long COVID by 40-60%; however, it does not eliminate it completely, which has driven the investigation of more targeted therapeutic approaches.[12,13] At present, no approved treatment is available, although several medications are being evaluated in clinical trials (Table 1).

The antiviral nirmatrelvir/ritonavir (Paxlovid) has been shown to reduce the risk of long COVID by 26% when administered within the first five days of infection.[4] Another antiviral under investigation is molnupiravir; however, its use raises concerns due to its potential mutagenic effects.[1] Metformin, primarily used in the treatment of type 2 diabetes, has also demonstrated potential benefits, reducing the risk by 41% when administered early.[1]

The immunological dysfunction observed in patients with long COVID has also prompted the exploration of immunomodulatory agents aimed at reducing chronic inflammation and the long-term effects of SARS-CoV-2 infection. For example, one of the biologic agents evaluated by the National Institutes of Health (NIH) was infliximab.[2]

In addition, probiotics are being investigated as immunomodulatory adjuvants with antiviral effects. Certain probiotic species and strains have been shown to exert antiviral mechanisms of action, such as competitive inhibition of viral adherence or replication.[16]

Echa Marine®, a dietary supplement that has been clinically tested and approved by ANMAT (National Administration of Drugs, Foods, and Medical Devices; National Registry of Food Products [RNPA] N°. 07-007419), is designed to alleviate symptoms of long COVID.

Table 1. Summary of therapies under investigation for long COVID

Therapy	Example	Mechanism of Action	Evidence / Outcomes
COVID-19 vaccines	mRNA, viral vector	Prevention of infection and reduction of inflammation	↓ risk of long COVID by 40–60%[12,13]
Antivirals	Nirmatrelvir/ritonavir (Paxlovid)	Inhibition of viral protease	↓ risk by 26% when administered early[4]
	Molnupiravir	Induces mutations in the viral genome	Under evaluation; mutagenic concerns[1]
Antidiabetic agents	Metformin	Immunometabolic modulation; ↓ viral replication	↓ risk by 41% when administered early[1]
Immunomodulators / biologics	Infliximab	Anti–TNF-α monoclonal antibody; reduction of chronic inflammation	Ongoing clinical trials[2]
Probiotics	Various bacterial strains	Immunomodulation; inhibition of viral adhesion and replication	Experimental and early clinical studies[16]
Innovative supplements	Echa Marine® (spinochromes) Echa Marine (espinocromas)	Improvement of mitochondrial function; immune system support	Approved by ANMAT; clinical use in persistent symptoms[17]

Developed by ERISEA S.A. using Argentine technology, it incorporates sea urchin spinochromes to enhance mitochondrial function and strengthen the immune system, highlighting the potential of national scientific research to address global health challenges.[17]

Gut Microbiota

Several studies have demonstrated an association between the gut microbiota and long COVID. In affected patients, dysbiosis has been observed, characterized by a reduction in beneficial bacteria such as *Faecalibacterium prausnitzii* and an increase in pathogenic taxa, including Enterobacteriaceae. The ACE2 receptor expressed in intestinal epithelial cells facilitates SARS-CoV-2 entry, leading to alterations in the gut microbiota and gastrointestinal symptoms such as diarrhea, nausea, and abdominal pain. These effects are mediated by disruption of intestinal barrier integrity and subsequent bacterial translocation into the bloodstream, triggering systemic inflammation.[18,19]

Gut dysbiosis may also influence central inflammation through the gut-brain axis, contributing to cognitive impairment and other neurological symptoms, particularly in older adults.[20]

The use of probiotics and their metabolites may help restore gut microbiota composition, regulate intestinal barrier function, and modulate immune responses, thereby reducing inflammatory and oxidative stress.[19,21] Supplementation with synbiotics (a combination of prebiotics and probiotics) has been shown to alleviate symptoms such as diarrhea, dyspnea, and cognitive impairment, representing a promising approach to mitigating disease effects. However, further studies are needed to elucidate the precise mechanisms through which the gut microbiota influences recovery.[22]

Modulation of the gut microbiota may exert indirect antiviral effects in SARS-CoV-2 infection by supporting intestinal barrier repair and anti-inflammatory processes. In addition, some probiotic strains exhibit direct antiviral effects by inhibiting viral adhesion and replication.[23]

Transcriptomic Studies

Transcriptomics examines the complete set of ribonucleic acid (RNA), ranging from microRNAs to long noncoding RNAs, thereby enabling an understanding of how a single genome gives rise to diverse cell types and regulates gene expression. The principal techniques include microarrays, which quantify predefined sequences, and RNA sequencing (RNA-Seq) using next-generation sequencing (NGS) technologies, which allow comprehensive analysis of all transcripts.

The study of the transcriptome is essential not only for interpreting functional elements of the genome but also for understanding the origin and progression of various diseases.[24] The publication of the human genome in the early 2000s had a profound impact on this field. Furthermore, advances in bioinformatics and sequence-mapping tools have enabled not only the detection of transcript fragments but also the reconstruction of their full sequences.[24]

In patients with long COVID, persistent SARS-CoV-2 RNA has been detected, suggesting that residual viral replication contributes to ongoing symptoms. A study by Soraya Maria Menezes et al. identified biomarkers associated with symptoms such as anxiety and depression.[25] Transcriptomic analysis revealed the presence of viral RNA, particularly in genes encoding the nucleocapsid protein (N), ORF7a, ORF3a, and an antisense RNA of ORF1ab, indicating active viral replication. These patients also exhibited reduced immunometabolic activity.[25]

Several studies have shown that individuals with prolonged SARS-CoV-2 infection have a 50% higher likelihood of developing long COVID compared with those with nonpersistent infection. In some individuals, viral amino acid substitutions have been identified, including mutations present in different SARS-CoV-2 variants. Notably, recurrent mutations have been observed in immunocompromised individuals, as well as mutations with immune-evasive properties.[26]

Biomarkers

The United States has invested USD 1.5 billion in research on long COVID, with the aim of identifying prognostic and therapeutic biomarkers. Forty-four (44) of its 50 states have established specialized clinics for patients with long COVID, and other countries have followed this example. This research is essential for improving clinical management and for understanding the long-term sequelae of viral infections.[27]

Salivary biomarkers in children

Saliva has been proposed as a promising biological matrix for studying physiological changes associated with long COVID in children, owing to its ease of collection and its safe, noninvasive nature.[28] A recent study by Tyrkalska et al. analyzed saliva samples from 49 affected children and 56 age-matched healthy controls, evaluating 13 biomarkers selected for their ability to reflect redox status, immune response, acute stress, and overall homeostatic balance.[29] (Table 2).

In symptomatic children, increased levels of the oxidative biomarkers TOS and d-ROM were observed, whereas antioxidant markers such as TEACH, CUPRAC, and FRAP were significantly reduced, indicating redox imbalance. By contrast, AOPP showed no significant variation. With respect to immune response, only ADA2 and total ADA (tADA) exhibited significant changes. In addition, levels of salivary α-amylase (sAA) and total proteins were decreased.

The results indicate that the levels of most salivary biomarkers and their correlation patterns differ significantly between children with long COVID and healthy controls, suggesting potential utility for distinguishing between these groups. In particular, the combination of TOS, ADA2, total proteins, and AOPP may allow reliable discrimination, whereas total proteins and ADA1 could differentiate between mild and severe symptoms. Furthermore, salivary biomarker levels were found to correlate with demographic and clinical parameters in this population.

Biomarkers of Neurological Involvement

Another group of biomarkers under investigation includes neuron-derived extracellular vesicles (nEVs). These nanoparticles, secreted by neuronal cells, contain specific proteins that reflect the physiological or pathological state of their cells of origin.[30] nEVs are isolated from plasma through a purification process using anti-L1CAM monoclonal antibodies, enabling targeted studies of neurological diseases.

The relevance of these vesicles lies in their ability to act as biomarkers in brain disorders, particularly in conditions in which they cross the blood–brain barrier and convey signals of neuronal alterations. This is especially relevant in the context of neurological sequelae of long COVID, where nEVs exhibit proteins indicative of neuronal dysfunction, such as beta-amyloid and pTau181, among others (Table 3).[30]

Neurological consequences of long COVID encompass a range of symptoms affecting the nervous system of patients who have recovered from the acute phase of COVID-19. These symptoms include chronic fatigue, brain fog, sleep disturbances, persistent headaches, mood disorders, and sensory alterations.[30]

In a study conducted by Tang N et al., protein levels in nEVs were analyzed across three groups: patients with neurological sequelae, recovered patients without persistent symptoms, and prepandemic healthy controls. All analyzed proteins, except Aβ40, were significantly elevated in the nEVs of patients with neurological sequelae compared with prepandemic healthy controls. In contrast, among recovered patients without persistent

Table 2. Salivary biomarkers selected for the study of long COVID in children

Redox status	Total oxidant status (TOS); Advanced oxidation protein products (AOPP); Derivatives of reactive oxygen metabolites (d-ROM); Trolox equivalent antioxidant capacity in the hydrophilic fraction (TEACH); Cupric reducing antioxidant capacity (CUPRAC); Ferric reducing ability of plasma (FRAP)
Immune response	Adenosine deaminase (ADA); Adenosine deaminase isoenzymes (ADA1 and ADA2); Total ADA (tADA); Ferritin; Anti–SARS-CoV-2 RBD IgG (IgG-RBD)
Acute stress	Salivary alpha-amylase (sAA)
General homeostatic status	Total proteins E

Table 3. Function of proteins measured in neuron-derived extracellular vesicles (nEVs

Abbreviation	Name	Function
Aβ40	*Beta-amyloid 1–40*	Involved in neuronal injury repair and synaptic signaling processes
tTau	*Total tau*	Stabilizes microtubules in neurons; essential for intracellular transport and neuronal cytoskeletal integrity
Aβ42	*Beta-amyloid 1–42*	Similar to Aβ40; involved in neuronal signaling and homeostatic processes
FGF-21	*Fibroblast growth factor 21*	Hormone with metabolic effects; regulates glucose and lipid homeostasis and promotes tissue repair
KLK-6	*Kallikrein 6*	Involved in extracellular protein degradation and tissue remodeling
NCAM-1	*Neural cell adhesion molecule 1*	Cell adhesion molecule involved in synapse formation and synaptic plasticity
NRGN	*Neurogranin*	Involved in synaptic signaling and cerebral plasticity; regulates memory capacity
pTau181	*Tau phosphorylated at position 181*	Phosphorylated tau variant that dynamically regulates its interaction with microtubules

symptoms, Aβ40 levels were significantly elevated compared with controls.

Furthermore, nEVs from patients with neurological sequelae exhibited significantly increased levels of neuronal proteins, including Aβ42, FGF-21, KLK-6, NCAM-1, NRGN, pTau181, TDP-43, total tau (tTau), and HMGB1, compared with prepandemic healthy controls.[30]

In conclusion, patients with long COVID and neurological sequelae demonstrated a significant elevation of proteins associated with neurodegeneration. In recovered patients without persistent symptoms, these differences were less pronounced, underscoring the specific relevance of these biomarkers in the presence of neurological involvement.[30]

DISCUSSION

Long COVID, defined by the persistence of symptoms beyond three months after acute SARS-CoV-2 infection, poses significant challenges due to its broad clinical heterogeneity and the multiple pathogenic pathways involved. Underlying mechanisms such as viral persistence, immune dysfunction, chronic inflammation, and alterations in the gut microbiota have been extensively investigated. These processes are associated with the reactivation of latent viruses, vascular and neuronal inflammation, as well as neuroendocrine and immune system dysregulation. In addition, the dysregulation of key cytokines, such as IL-6, plays an important role in disease progression, particularly in patients with preexisting conditions or underlying immune impairment.

Symptoms such as fatigue, cognitive dysfunction, and respiratory disorders substantially impair patients' quality of life, underscoring the need for a comprehensive and multidisciplinary medical approach. Recent studies have also indicated that long COVID affects children and adolescents, with symptoms predominantly related to mood disturbances and cognitive difficulties. This scenario reinforces the importance of preventive strategies such as vaccination, which not only reduces the severity of acute infection but also lowers the risk of developing long COVID. However, vaccination alone does not fully eliminate this risk, highlighting the need to explore targeted therapeutic interventions. Therapeutic advances include antivirals such as nirmatrelvir/ritonavir, which have shown promising results in reducing symptoms when administered during the early stages of infection. In addition, agents such as metformin, immunomodulatory drugs, and probiotics have emerged as potential tools in the management of this condition, although further studies are required to confirm their long-term efficacy and safety.

The gut microbiota plays a critical role in the pathophysiology of long COVID, as intestinal dysbiosis not only compromises intestinal barrier integrity but also contributes to systemic inflammation and neurocognitive symptoms. Accordingly, modulation of the microbiome through the use of synbiotics has emerged as a promising therapeutic strategy, although it remains at an early stage of investigation.

CONCLUSION

Long COVID is a multifactorial condition with significant implications for global health. Despite advances in the understanding of its underlying mechanisms and the emergence of therapeutic options, substantial knowledge gaps remain. The development

of preventive strategies and targeted therapies, together with multidisciplinary approaches that address the comprehensive management of symptoms, is essential to effectively confront this condition. Furthermore, continued support for scientific research –illustrated by the potential of national innovations such as the dietary supplement Echa Marine– underscores the need to further promote knowledge generation in order to improve patients' quality of life.

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