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Long-COVID, Metabolic and Endocrine Disease

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ABSTRACT

In the aftermath of the corona pandemic, long-COVID or post-acute COVID-19 syndrome still represents a great challenge, and this topic will continue to represent a significant health problem in the coming years. At present, the impact of long-COVID on our health system cannot be fully assessed but according to current studies, up to 40 % of people who have been infected with SARS-CoV-2 suffer from clinically relevant symptoms of long-COVID syndrome several weeks to months after the acute phase. The main symptoms are chronic fatigue, dyspnea, and various cognitive symptoms. Initial studies have shown that people with overweight and diabetes mellitus have a higher risk of developing long-COVID associated symptoms. Furthermore, repeated treatment of acute COVID-19 and long-COVID with steroids can contribute to long-term metabolic and endocrine disorders. Therefore, a structured program with rehabilitation and physical activity as well as optimal dietary management is of utmost importance, especially for patients with metabolic diseases and/or long-COVID. Furthermore, the removal of autoantibodies and specific therapeutic apheresis procedures could lead to a significant improvement in the symptoms of long-COVID in individual patients.

Introduction

Recent epidemiological studies, such as the Gutenberg Long-COVID study in Germany (https://www.unimedizin-mainz.de/gcs/), show the immense consequences that long-COVID could have for our health system. According to this, up to 40 % of those affected stated that they still had residual symptoms of COVID-19 six months after the infection. Every third person with a SARS-CoV-2 infection complained that after six months they were not as pro-

ductive as before the illness. The list of possible symptoms is very extensive and ranges from exhaustion, shortness of breath, headaches, sleep disorders, lack of concentration to cognitive problems, skin rashes, diarrhea, and tinnitus [1–3]. Recently, an S1 guideline on post/long-COVID was drawn up by various German and Austrian medical societies [4]. According to the Cochrane Rehabilitation Review [5], a post/long-COVID diagnosis can be assumed if one of four criteria is present: 1) Symptoms that persist from the acute COVID-19 phase or its treatment, 2) Symptoms that have led to a new health restriction, 3) New symptoms that have occurred after the end of the acute phase but are understood to be a consequence of COVID-19, or 4) Worsening of a pre-existing underlying condition. Based on an extensive literature review, a new guideline for the long-term effects of COVID-19 was also drawn up by the British health authority (National Institute for Health and Care Excellence (NICE) in December 2021. Here, long-COVID was defined as signs and symptoms that develop during or after infection with COVID-19 and last longer than 12 weeks and cannot be explained by any other diagnosis [6].

A study from King's College London, in which 4000 patients with COVID-19 prospectively documented their symptoms in an app, identified criteria for early prediction of their risk to develop long-COVID. Across countries and ethnic backgrounds, obese, older and female patients, and those requiring hospitalization were most at risk of developing long-COVID [7]. Another study from Norway showed that even patients with a milder form of COVID-19, who had isolated themselves at home, often developed symptoms of long-COVID. It showed that 52 % of young adults between the ages of 16 and 30 who were self-isolated still had symptoms after 6 months; 28 % continued to have a disturbance of taste and smell, 21 % still felt tired and exhausted, 13 % had dyspnea, 13 % had difficulty concentrating, and 11 % had difficulty remembering [8].

What is the relationship between long-COVID and diabetes?

An infection with SARS-CoV-2 can induce or aggravate clinical diabetes mellitus type 1 (T1DM) and type 2 (T2DM) [9–12]. After infection with SARS-CoV-1, it was shown that metabolic derangement was still detected in fully recovered patients up to 12 years after the infection [13]. Compared to healthy controls, there were significant differences in the metabolome in these patients. In particular, there were significant changes in lipid metabolism [13]. On the other hand, it was striking that after the SARS-CoV-1 infection, diabetes that had evolved during the acute illness completely regressed in many patients.

We have set up an international registry CoviDIAB (https://covidiab.e-dendrite.com) to follow up on patients with diabetes who have emerged during the current pandemic [14]. This registry will provide evidence if and to what extent T1DM or T2DM presenting in the framework of acute SARS-CoV-2 infection may regress in the post-infectious observation interval. Intriguingly, some patients may develop diabetes for the first time in the long-COVID phase.

Infection and inflammation are potent drivers of diabetes. Moreover, steroid administration deserves our attention. An 8–10 days course of dexamethasone is routinely administered to patients with severe COVID-19, and many patients with long-term damage to the lung parenchyma continue to receive steroid treatments over a protracted period of time. Therefore, steroid-induced metabolic deterioration and steroid-induced diabetes in these patients is not unexpected. This has been also observed in our clinic. After extensive use of steroids for several weeks to treat COVID-19, the administration is abruptly stopped, which in some cases have led to acute adrenal insufficiency.

Following COVID-19, many patients exhibit autoimmune disorders resulting in the prolonged therapeutic use of steroids, enhancing risks of metabolic side effects. This situation could get even worse in the coming months and years, as the new drugs that are now approved for the treatment and prevention of a severe course of COVID-19 might increase the steroid-related metabolic adverse effects. A notable example is protease inhibitors that prevent serine protease-mediated proteolysis of spike glycoproteins of the SARS-CoV-2 virus [15]. One drug of this class, Nirmatrelvir is combined with the long-known generic HIV drug Ritonavir, which is supposed to increase the therapeutic effect. Similar to steroids, these drugs are metabolized in the liver by the cytochrome P450 (CYP3A4) enzyme system [16]. When steroids are administered concurrently to Nirmatrelvir/Ritonavir, this may lead to Cushing-like changes and, under certain circumstances, to the occurrence of adrenal insufficiency after discontinuation of the steroids as previously observed in patients with HIV [17].

Patients with metabolic syndrome receiving other medications that are broken down via the CYP3A4 enzyme system, for example antihypertensive agents, such as calcium channel antagonists, or anti-dyslipidemic agents, such as statins, should expect an increased effect in the acute phase and must be closely monitored. On the other hand, accumulating evidence suggest that SARS-CoV-2 mediated reprograming of cholesterol metabolism results in the upregulation of the expression of several lipid synthesis modulators (including SREBP1/2, CD36, PPARγ or DGAT-1) leading to the production of cholesterol and lipid droplets. A reduction in cholesterol synthesis through the blockade of this pathway can decrease both the viral replication and the inflammatory response induced by SARS-CoV-2 [18]. Also, the enzyme cholesterol 25-hydroxylase that depletes cholesterol from plasma membrane is upregulated during SARS-CoV-2 infection which is believed to restrict viral internalization to the cell [19].

Since we were recently able to show that SARS-CoV-2 could be detected in the adrenals of patients that died due to COVID-19 and that the virus is able to infect adrenal cells in vitro, it must be assumed that the adrenal glands can be damaged in the context of COVID-19 [20]. If patients now receive these new antiviral substances in the acute phase together with repeated doses of steroids, this may lead, after steroid withdrawal, to a new form of secondary adrenal insufficiency with symptoms similar to those of long-COVID, such as fatigue, exhaustion, blood pressure dysregulation, lack of concentration and depression [21].

Do patients with diabetes have a higher risk of long-COVID?

So far, the course of the pandemic has shown very clearly that patients with obesity, diabetes, and metabolic syndrome belong to the main risk groups for the development of a severe course including a fatal outcome of COVID-19. A significant number of people that died from COVID-19 suffered from pre-existing diabetes with

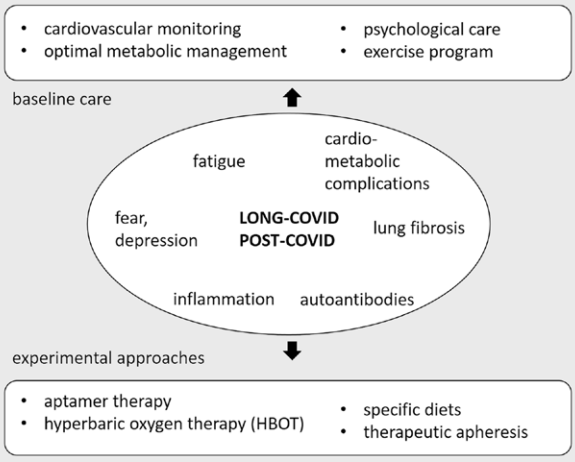
or without obesity and hypertension [12]. Recent data demonstrated that the same group of patients are at an increased risk of long-COVID symptoms. Studies have shown, for example, that type 2 diabetics in particular have a high prevalence of post-COVID fatigue [22]. One scenario can be attributed to the increased glycolytic activity in inflammatory cells such as macrophages which exacerbate viral load and increase proinflammatory cytokine production resulting in more epithelial damage, lung fibrosis and T helper lymphocyte dampening [23]. Post-COVID fatigue syndrome in patients with pre-existing diabetes is also associated with reduced muscle strength [24]. The reduced muscle strength may indicate the presence of sarcopenia, which is, of course, more common in patients with poorly controlled diabetes. This shows that, especially for patients with diabetes in the post-COVID phase, appropriate glycemic control and an adequate nutritional status are of great importance to ensure rapid recovery. In addition to fatigue, these patients with T2DM and long-COVID also experienced weight loss and significantly reduced physical activity. On the other hand, there are also reports of excessive food intake and weight gain in patients with long-COVID [24]. Yet, an other case control study of hospitalized patients showed no difference between the occurrence of long-COVID symptoms and the presence of diabetes. In this study, it was pointed out that a diabetic metabolic status plays a more important role in the acute phase of the COVID-19 than in the post-COVID phase. Nevertheless, the authors emphasize that further longitudinal studies are needed to confirm these assumptions [25]. Another international study showed both acute and long-lasting glycemic disorders in patients after SARS-CoV-2 infection [26].

Long-term metabolic changes must therefore also be assumed in the post-acute phase of COVID-19 [27]. The relationship between COVID-19 and diabetes-related metabolic derangement is certainly a mutually reinforcing vicious circle. On one hand, the inflammation in acute COVID-19 disease leads to a lasting deterioration in the metabolic situation; on the other hand, diabetes is a state of chronic inflammation with changes in the innate and adaptive immune system that enhance and accentuate symptoms of long-COVID. It is therefore not surprising that poorly controlled diabetes has been described as a risk factor for post-COVID lung fibrosis [28].

What can we do?

Overall, it can be assumed that poorly controlled diabetes mellitus is not only a significant risk factor in the acute phase of COVID-19 and vaccination failure, but also for symptoms and complications in the post-COVID phase. Therefore, patients in the post-COVID phase must be early monitored and optimally managed, focusing on appropriate glycemic and lipid profile control [29]. An adequate metabolic adjustment not only leads to a positive influence on long-term complications, such as pulmonary fibrosis, but also minimizes the development of tiredness, exhaustion and fatigue syndromes. Checking and monitoring the metabolic status must therefore be an integral part of any clinical monitoring of a post-COVID outpatient clinic.

Since patients with diabetes mellitus often have established cardiometabolic disorders such as atrial fibrillation, sarcopenia, muscle fatigue and microvascular endothelial disorders, the deterioration of these complications of diabetes in the acute and post-acute phase of COVID-19 is to be expected. Therefore, strict control of diabetes and its comorbidities with structured rehabilitation, physical activity and an optimal dietary adjustment are crucial for the management of the post-COVID phase (▶ **Fig. 1**).



▶ **Fig. 1** Management of long-COVID.

A healthy diet in the post-COVID phase can also help to alleviate it. Many experimental studies have shown that an unhealthy, high-fat diet increases susceptibility to various infectious diseases [30]. For example, experimental animals on a high-fat diet had a two-fold increase in mortality with increases in lung changes and inflammatory cytokines in influenza infection compared to animals on a normal diet. The proportion of fat in the diet can therefore influence the course of viral diseases. Diets rich in omega-3 fatty acids promote the formation of anti-inflammatory proteins, which can have a positive effect on lung and organ damage. Numerous studies have shown that dietary supplementation with the short-chain fatty acids propionate and butyrate, supplementation with vitamins and minerals such as zinc, and administration of acetyl-CoA carboxylase isoforms, such as ACC1 and carnitine palmitoyl transferase 1 inhibitors, reduce the long-term damage caused by viral-induced inflammation [30]. Thus, long-term consequences caused by COVID-19 could be positively affected by a targeted change of our own metabolism through microbiota and dietary strategies. Dietary supplementation with tryptophan or glutamine supplementation has been suggested for the long-COVID phase [25, 31–35]. Such approaches need to be further investigated in larger, controlled studies. Further promising impacts on treatment, especially for fatigue in post-COVID patients, are based on a new active ingredient BC 007 from the Berlin start-up company Berlin Cures, which is currently being tested in clinical studies at the University of Erlangen. This is an unmodified DNA aptamer, which was initially developed without reference to long-COVID. This aptamer acts as a binding partner for autoimmune antibodies directed against G protein-coupled receptors. Since BC 007 also binds antibodies directed against α1-adrenoceptor, β1-adrenoceptor,

β2-adrenoceptor, and endothelin A receptors, this drug was tested for the therapy of cardiomyopathies. Patients with chronic fatigue syndrome often have high antibody titers against these receptors, which could explain symptoms of chronic fatigue up to and including postural hypertension. Thus, BC 007 is now in phase II clinical trials for fatigue syndrome. It is not yet known how the metabolism is influenced by this approach.

Interestingly, many patients with the classic symptoms of long-COVID including chronic fatigue report an improvement in their condition after the use of therapeutic apheresis. In Germany, therapeutic apheresis is mainly used in specialized centers for severe lipid disorders [36]. These are patients with very high LDL and LPa levels that cannot be treated as effectively with any other therapeutic approach. The mechanism of action by which an extracorporeal apheresis procedure could have a positive impact on the course of long-COVID syndrome has not yet been fully elucidated. It is clear that after therapeutic apheresis, metabolic parameters, in particular the lipid values, can be significantly improved and reduced by up to 80 %. In addition, an anti-inflammatory effect is achieved by a significant reduction in C-reactive proteins and other pro-inflammatory peptides and cytokines [37, 38]. Finally, extracorporeal apheresis achieves a significant reduction in immunoglobulins and autoantibodies. Another effect could be an improvement in blood circulation and the function of the red blood cells, whereby the oxygen content of the blood carriers is also optimized in the brain, with an improvement on "brain fog", a classic symptom reported by patients with post-COVID. The effects of therapeutic apheresis on the autoimmune process, anti-inflammatory and rheological changes in post-COVID patients are currently being investigated in various clinical studies.

Conclusion

The current SARS-CoV-2 pandemic and its metabolic aftermath compound the global challenges already presented by metabolic disease. Timely efforts to gain a deeper understanding of the underlying pathophysiology must readily be translated into improved multidisciplinary care delivered by expert teams of diabetologists, endocrinologist, and general practitioners to ensure best outcomes. Ultimately, we need to advance new concepts to achieve better immunological, metabolic and nutritional control. Furthermore, in order to optimize planning and provision of health care, research is required to decipher the early biomarkers and predictors of long-COVID.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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