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Research Article

Explaining Long COVID: A Pioneer Cross-Sectional Study Supporting the Endocrine Hypothesis

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Abstract

Context: In some patients, symptoms may persist after COVID-19, defined as long COVID. Its pathogenesis is still debated and many hypotheses have been raised.

Objective: Our primary objective was to evaluate the corticotroph and somatotroph functions of patients previously infected with SARS-CoV-2 and experiencing post–COVID-19 syndrome to detect any deficiencies that may explain long COVID.

Methods: A cross-sectional study was conducted including patients who had previously contracted SARS-CoV-2 with a postinfection period of 3 months or less to 15 months, divided into 2 groups. The first group (G1) comprised fully recovered patients, while the second group (G2) included patients experiencing long COVID. The primary outcome was the comparison of corticotroph and somatotroph functions.

Results: A total of 64 patients were divided into 2 groups, each consisting of 32 patients. G2 exhibited more frequently anterior pituitary deficits compared to G1 ($P = .045$): for the corticotroph axis (G1: 6.3% vs G2: 28.1%) and for the somatotroph axis (G1: 31.3% vs G2: 59.4%). Baseline cortisol level was significantly lower in G2 (G1: 13.37 µg/dL vs G2: 11.59 µg/dL) ($P = .045$). The peak cortisol level was also lower in G2 (G1: 23.60 µg/dL vs G2: 19.14 µg/dL) ($P = .01$). For the somatotroph axis, the insulin growth factor-1 level was lower in G2 (G1: 146.03 ng/mL vs G2: 132.25 ng/mL) ($P = .369$). The peak growth hormone level was also lower in G2 (G1: 4.82 ng/mL vs G2: 2.89 ng/mL) ($P = .041$).

Conclusion: The results showed that long COVID patients in our cohort were more likely to have anterior pituitary deficiencies. The endocrine hypothesis involving anterior pituitary insufficiency can be considered to explain long COVID.

Key Words: COVID-19, SARS-CoV-2, hypopituitarism, central adrenal insufficiency, GH deficiency, insulin tolerance test

Abbreviations: ACE2, angiotensin 2–converting enzyme; ACTH, adrenocorticotropin; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin growth factor-1; IGFBPs, IGF-1 binding proteins; ITT, insulin tolerance test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ST, Synacthen test; WHO, World Health Organization.

The most recent pandemic reported to date is COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for this disease [1, 2].

To date, more than 769 million individuals worldwide have been infected with COVID-19, resulting in more than 6.9 million deaths, as documented by the World Health Organization (WHO) [1, 3]. SARS-CoV-2, similar to other coronaviruses, enters host cells via the angiotensin 2–converting enzyme (ACE2) receptor and the transmembrane serine protease 2 [4].

COVID-19 infection has been associated with hypothalamo-pituitary impairments, such as pituitary apoplexy, diabetes insipidus, or hypophysitis [5-10]. Apart from the ongoing global effect of the virus, the long-term consequences of SARS-CoV-2 infection remain largely unknown. Many patients have reported the persistence or emergence of certain symptoms several months after the initial viral infection [11].

This has led to the recognition of a novel clinical entity known as "post–COVID-19 syndrome," commonly referred to as "long COVID" [12]. The prevalence of post–COVID-19 syndrome among patients varies widely, ranging from low percentages to affecting up to 93% of individuals who have been infected with SARS-CoV-2 [13, 14].

Various virological and histological hypotheses exploring these lingering symptoms suggest the persistence of certain postinflammatory lesions, particularly vascular ones [15]. However, a closer examination of the residual symptoms experienced by these patients reveals that some closely resemble the symptoms associated with anterior pituitary deficiencies, particularly corticotroph or somatotroph [6].

Recently, certain authors have proposed the involvement of the pituitary gland in post–COVID-19 syndrome [6, 15]. This is because the ACE2 receptor, which facilitates SARS-CoV-2

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entry into cells, is expressed within the hypothalamo-pituitary axis [6]. The precise mechanisms by which the virus acts on infected cells remain subject to debate, but inflammatory and autoimmune processes are considered the most likely culprits [6, 16].

The evaluation of the pituitary gland during the acute phase of infection and during the follow-up of post–COVID-19 patients has not been consistently implemented due to the insidious nature of these lesions [6]. To the best of our knowledge, no study worldwide has assessed the hypothalamo-pituitary axis of patients with post–COVID-19 syndrome using an insulin tolerance test (ITT) [17].

The aim of this study was therefore to assess the anterior pituitary functions of individuals previously infected with SARS-CoV-2 who continue to experience post–COVID-19 syndrome to identify potential deficiencies that could account for the persistence of certain symptoms several months after the viral infection.

Materials and Methods

This cross-sectional study was conducted within the Endocrinology & Diabetology Department of Farhat Hached University Hospital in Sousse, Tunisia, from January to December 2022. The study received approval from the local ethics committee (2023/363). It included 64 adult patients who had previously contracted SARS-CoV-2, divided into 2 groups, each consisting of 32 patients. The first group (G1) comprised fully recovered patients, while the second group (G2) included patients experiencing post–COVID-19 syndrome. Written and informed consent was obtained from the patients for publication.

Inclusion Criteria

- Adult patients who were previously infected with SARS-CoV-2 and have fully recovered (no post–COVID-19 syndrome) with a postrecovery period of 3 months to 15 months (an approximate time frame for the recovery of the pituitary adrenal axis) [11].
- Adult patients who continue to experience post–COVID-19 syndrome with a postinfection period of 3 months or less than 15 months.
- Documented SARS-CoV-2 infection.

Exclusion Criteria

- Lack of confirmation of SARS-CoV-2 infection.
- Contraindications to the ITT: age older than 65 years, ischemic or arrhythmic heart disease, pregnancy, breastfeeding, history of stroke or epilepsy [18].
- Any organic pathology, ongoing infection, or medication that may interfere with hormonal assessments during or before the infection disease (such as steroid intake).

Patients with long COVID were recruited based on the WHO Delphi consensus [14].

Infection was documented through a positive reverse-transcription polymerase chain reaction test, rapid antigen test, or a thoracic computer tomography scan confirming lung lesions indicative of COVID-19 [19, 20].

The clinical severity of SARS-CoV-2 infection was assessed according to the National Institute for Health and Care Excellence [21] as follows: asymptomatic, mild (no pneumonia, mild dry cough, malaise, headache, muscle pain, anosmia, ageusia, no dyspnea), moderate (pneumonia without severe symptoms, such as cough, mild dyspnea, respiratory rate < 30 breaths per minute, oxygen saturation $\geq 94\%$), severe (dyspnea, respiratory rate ≥ 30 breaths per minute, or oxygen saturation $< 94\%$ on room air), and critical (vital distress, shock, septicemia, organ failure, and/or the need for invasive or noninvasive respiratory support).

Assessment of Pituitary Functions

Basal state hormone levels

Basal levels of the following hormones, insulin-like growth factor-1 (IGF-1), and adrenocorticotropin (ACTH), were measured at 8 AM for all participants.

Insulin tolerance test

The assessment of the corticotroph and somatotroph axes was performed using an ITT. It was conducted by administering a bolus intravenous injection of 0.15 U/kg of regular human insulin (Actrapid). Blood samples for measuring serum cortisol, growth hormone (GH), and blood glucose levels were obtained at the baseline, at the time of symptomatic hypoglycemia and at 10, 20, 30, 60, 90, and 120 minutes afterward [22]. Only patients with confirmed hypoglycemia (serum glucose level ≤ 2.2 mmol/L) were included in the study.

Definitions of corticotroph and somatotroph deficiencies

The corticotroph axis was assessed using basal cortisol and ACTH levels along with cortisol levels during the ITT. Corticotroph deficiency was defined by a peak cortisol level less than 18 µg/dL during the ITT, associated with an ACTH level less than 50 pg/mL [23].

The somatotropin axis was evaluated based on the basal serum levels of IGF-1 and GH levels during the ITT. The diagnosis of severe somatotropin deficiency was made in the absence of a response to the ITT, with a peak GH level of less than 3 ng/mL in adults [24]. Only severe somatotropin deficiencies were considered in this study since, according to recommendations, only GH levels less than 3 ng/mL indicate the need for hormone replacement therapy [25].

Analytical Methods

The serum levels of various hormones were measured using the radioimmunoassay method with a commercially available kit (Beckman Coulter) with a sensitivity of 0.2 µg/dL for cortisol and a sensitivity of 0.1 ng/mL for GH. The intra-assay and interassay coefficient of variation were 9% and 5.8%, respectively for cortisol and 7.1% and 2.1% for GH.

Statistical Analyses

Statistical analysis was performed using IBM SPSS version 25.0 (IBM Inc). The normality of distribution was assessed using the Kolmogorov-Smirnov test. The *t* test was used to compare normally distributed quantitative variables. When the distribution was not normal, the Mann-Whitney test was employed. Depending on the distribution, data were expressed as mean ± SD. The chi-square test was used for qualitative variables. The association between 2 quantitative variables was

Table 1. Comparison of personal history and clinical parameters between the two groups

Personal history and clinical parameters	G1 (n %)	G2 (n %)	*P*
Type 2 diabetes, mean (SD)	9 (28.1)	6 (18.8)	.248
Vaccination, mean (SD)	28 (87.5)	29 (90.6)	.689
Corticosteroid intake during COVID-19	10 (31.3)	8 (25)	.578
Hypertension, mean (SD)	7 (21.9)	5 (15.6)	.522
Cardiovascular disease, mean (SD)	0 (51)	0 (51)	—
Body mass index, mean (SD)	28.37 (5.39)	28.63 (7.36)	.872
Obesity, mean (SD)	13 (40.6)	13 (40.6)	.377
Bradycardia, mean (SD)	0	2 (6.3)	.72
Dyspnea, mean (SD)	3 (9.4)	9 (28.1)	.06
Glycemia, mean (SD) (mmol/L)	5.8 ± 0.99	5.47 ± 1.37	.214
Goiter, mean (SD)	1 (3.1)	1 (3.1)	≥.999
Depilation, mean (SD)	2 (6.3)	5 (15.6)	.280
Low blood pressure, mean (SD)	2 (6.3)	4 (12.5)	.391
Orthostatic hypotension, mean (SD)	4 (12.5)	3 (9.4)	.689

assessed using the Pearson correlation coefficient. Dispersion analysis between the 2 tests and hormone response graphs were generated using SPSS version 25.0 software. The statistical significance threshold (*P*) was set at 5%.

Results

Patients

G1 was composed of 14 men and 18 women, while G2 was composed of 9 men and 23 women. The mean age of our patients was 43.31 ± 14.30 in G1 vs 42.56 ± 13.45 in G2. The distribution of sexes, mean age, and family and personal history was comparable between both groups (Table 1). The majority of patients in the 2 groups received vaccination against SARS-CoV-2 but after their first contamination by the SARS-CoV-2 (G1: 87.5% vs G2: 90.6%) ($P = .689$).

The most frequently encountered type of vaccine in both groups was the Pfizer vaccine (G1: 56.3% vs G2: 68.8%) ($P = .302$).The time interval for hormonal assessment in months was comparable between the 2 groups, with a median of 11.5 months (Q1-Q3) = (9-14) for G1 and 11 months (Q1-Q3) = (6-14) for G2 ($P = .498$). A higher proportion of patients in G1 had been hospitalized (G1: 59.3% vs G2: 28.1%) ($P = .04$). Patients in G2 had a significantly higher number of SARS-CoV-2 infection episodes, with a median of 1 (Q1-Q3) = (1-1) for G1 vs a median of 2 (Q1-Q3) = (1-2) for G2 ($P = .01$). The severity of COVID-19 infection was statistically comparable between the 2 groups ($P = .624$). Corticosteroid therapy was more frequently prescribed in G1 compared to G2 (G1: 50% vs G2: 21.8%; $P = .019$), with comparable average doses and durations between the 2 groups ($P = .61$) and ($P = .23$), respectively.

Fatigue and cognitive disturbances were the most frequently identified symptoms of post–COVID-19 syndrome within G2, with rates of 84.4% and 93.8%, respectively. Cognitive disturbances encompassed concentration and memory problems, affecting 78.1% and 68.8% of G2, respectively. Dizziness was present in 37.5% of cases (Fig. 1).

Evaluation of Insulin Tolerance Test

All patients exhibited venous blood glucose levels less than or equal to 2.2 mmol/L. The mean nadir glucose obtained at different time points during the test was 1.87 ± 0.31 mmol/L for G1 and 1.76 ± 0.44 mmol/L for G2 ($P = .360$). The nadir glucose level was most frequently observed during the 30th minute in both groups (G1: 40.5% vs G2: 46.9%) ($P = .625$).

Corticotroph Axis

Mean baseline cortisol level was significantly lower in G2 ($P = .045$) as opposed to that of G1 with mean levels of 13.37 ± 3.50 µg/dL in G1 vs 11.59 ± 3.53 µg/dL in G2. Mean ACTH was 22.47 ± 11.70 pg/mL in G1 vs 17.38 ± 12.60 pg/mL in G2 with a distribution tending toward statistical significance ($P = .07$).

For G2, the cortisol reached a mean peak of 19.14 ± 4.73 µg/dL, which was significantly lower than that of G1, which was 23.60 ± 5.56 µg/dL ($P = .01$), with the peak most commonly occurring at the 60th minute of the ITT in both groups. The cortisol kinetic curves during the ITT in both groups are depicted in Fig. 2.

Among the 64 patients, 17.2% exhibited a corticotroph deficiency. No peripheral adrenal insufficiency was identified in either group.

Within G1, 2 isolated corticotroph deficiencies were observed, accounting for 6.3% of the patients, compared to 9 corticotroph deficiencies within G2 (28.1%). The proportion of corticotroph deficiencies was significantly higher in G2 compared to G1 ($P = .02$) (Table 2). Among the patients with corticotroph deficiencies, only one had received glucocorticoid treatment during COVID-19.

Somatotropin Axis

The average IGF-1 level was 146.03 ± 64.58 ng/mL for G1 and 132.25 ± 64.07 ng/mL for G2, with a comparable distribution between the 2 groups ($P = .369$). During the ITT, the GH level in G1 reached an average peak of 4.82 ± 3.92 ng/mL, while G2

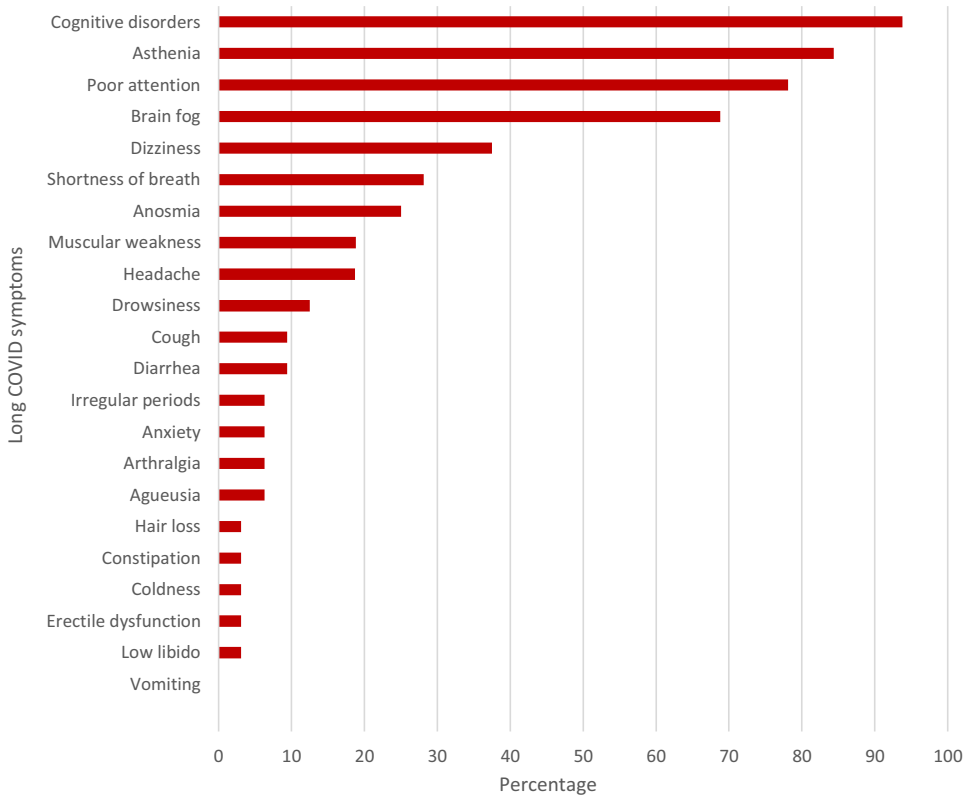

Figure 1. Long COVID symptoms in post-COVID syndrome patients.

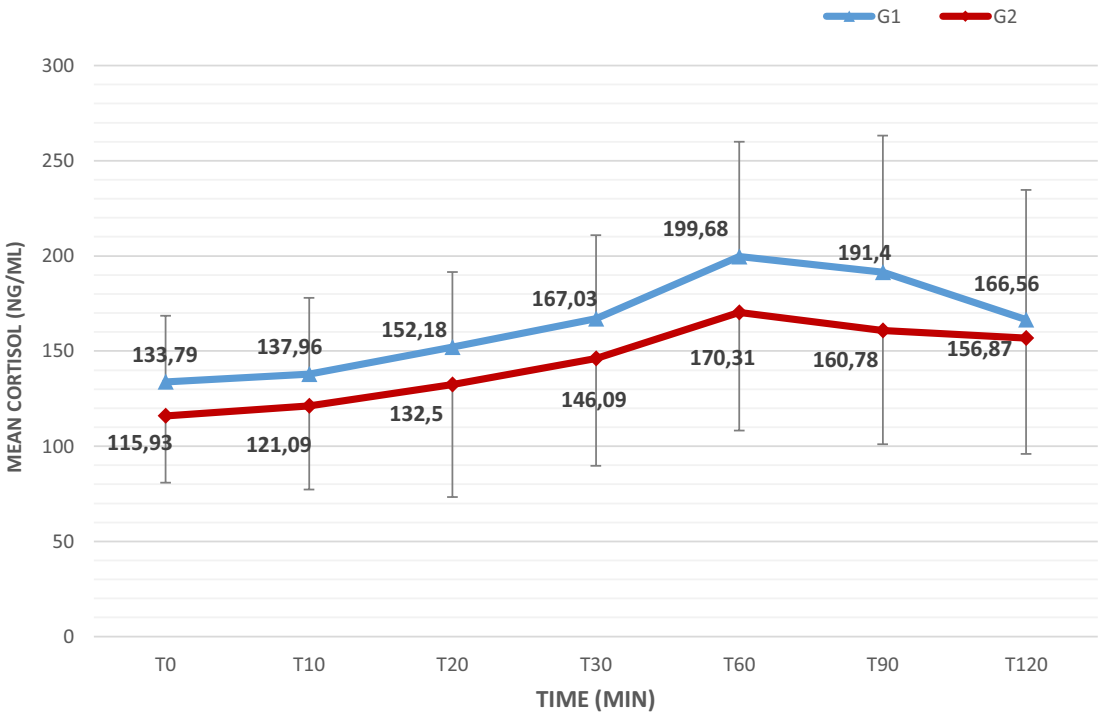

Figure 2. Mean cortisol level for each time in both groups during the insulin tolerance test.

had an average peak of 2.93 ± 3.5 ng/mL. The difference in the GH peak between the 2 groups was significantly lower in G2 ($P = .041$). The GH peak most often occurred at the 60th minute of the ITT in both groups. The curves depicting the GH kinetics during the ITT in both groups are shown in Fig. 3.

In our study population, 45.35% of the patients exhibited GH deficiency (GHD). Among the patients in G1, 10 cases

of somatotroph deficiency were identified, accounting for 31.3%, while in G2, 19 patients had GHD, representing 59.4% of the total patients. The proportion of GHD was significantly higher in G2 compared to G1 ($P = .02$) (see Table 2).

Combined Analysis of Different Anterior Pituitary Axis Impairments in Both Groups

Impairment in at least 1 of the 2 pituitary axis was diagnosed in 13 patients in G1, accounting for 40.6% of the patients, compared to 21 patients in G2, representing 65.6% of the patients. The proportion of patients with at least one anterior pituitary axis impairment was significantly higher in G2 ($P = .045$). Among patients with anterior pituitary axis impairment, most of patients in G1 had a single impairment (G1: 61.5% vs G2: 47.6%), whereas the majority of patients in G2 had impairment of both pituitary axes (G1: 38.5% vs G2: 52.4%) ($P = .587$).

Discussion

In the course of our study, we identified a higher frequency of GHD (G1: 31.3% vs G2: 59.4%) and corticotropic deficits (G1: 6.3% vs G2: 28.1%) among patients with long COVID.

Various studies have documented the presence of endocrine abnormalities during the acute phase of COVID-19. The hypothesis of the persistence of these abnormalities in long COVID has recently emerged [6, 26]. Our team further supported this hypothesis by commenting on a case from Aliberti et al [27], who isolated the virus in the pituitary tissue. Based on this finding, we conceived the idea for this study to investigate the persistence of the virus in the pituitary tissue as potentially responsible for the observed deficits and resulting in the lingering sequelae [27, 28].

There are very few studies with which we can directly compare our results. Urhan et al [16] evaluated 43 patients with results that are nearly comparable to ours: GHD and corticotropic deficits were identified in 46.5% and 16.2% of patients, respectively.

In comparison with other viral infections, Leow et al [29] identified corticotropic deficits in 39.4% of surviving patients of SARS-CoV. Wei et al [30], on the other hand, observed a decrease in immunostaining of corticotrophic, somatotropic, and thyrotropic cells in individuals infected with SARS-CoV. Due to the high genetic similarity between SARS-CoV and SARS-CoV-2, the hypothesis of COVID-19–related hypophysitis is strongly supported [8, 25, 31-35].

The development of hypophysitis in COVID-19 "long-haulers" may result from an excessive inflammatory or autoimmune process involving the pituitary gland [4, 8]. One supportive piece of evidence for autoimmunity is the presence of antipituitary and antihypothalamic antibodies in 75% of corticotropin-deficient patients, as demonstrated in the work of Gonen et al [36].

To explain why these pituitary lesions were not initially detected, the hypothesis of overprescription of corticosteroids is plausible. Indeed, during severe cases of COVID-19, high doses of dexamethasone were used in the majority of hospitalized patients [28, 37-40]. These corticosteroids may have inadvertently induced temporary remission of hypophysitis [41]. Since the treatment of autoimmune hypophysitis can last for several weeks, this prescription may have suppressed the inflammatory processes temporarily without curing them, allowing for the persistence of postinfectious symptoms [42].

Table 2. Comparison of corticotroph and somatotroph axis evaluation between the two groups

Corticotropic axis	G1 n (%)	G2 n (%)	*P*
Central adrenal insufficiency	2 (6.3)	9 (28.1)	.02
Normal corticotroph axis	30 (93.7)	23 (71.9)	.02
Somatotropic axis	**G1 n (%)**	**G2 n (%)**	***P***
Growth hormone deficiency	10 (31.2)	19 (59.4)	.02
Normal somatotroph axis	22 (68.8)	13 (40.6)	.02

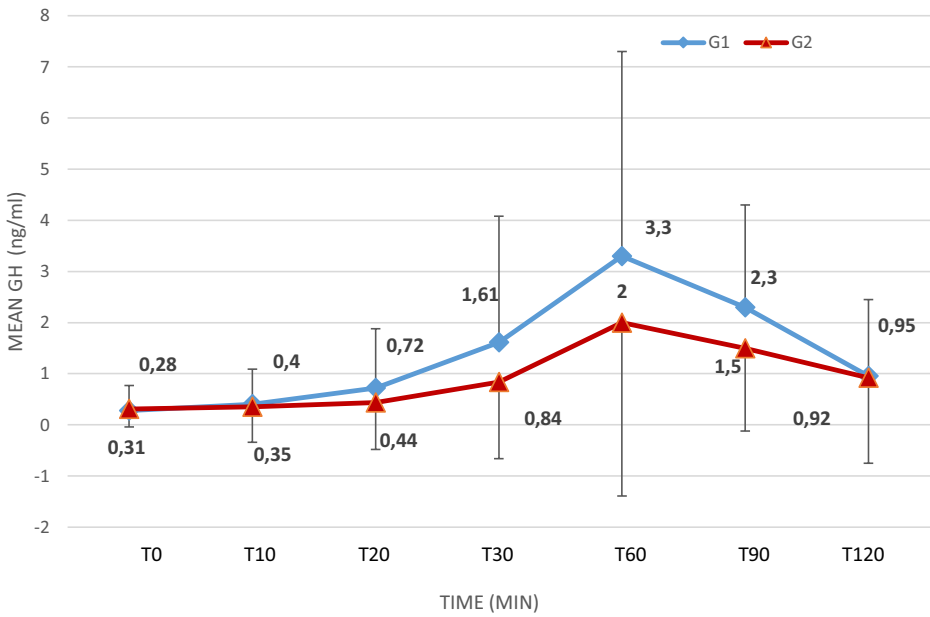

Figure 3. Mean growth hormone (GH) level for each time in both groups during the insulin tolerance test.

In our study, 17.2% of patients exhibited corticotropic deficiency, with the vast majority of these deficiencies being observed in COVID-19 long-haulers. Corticotropic deficiency typically presents with nonspecific symptoms, including profound fatigue, hypoglycemia, hypotension, and gastrointestinal disturbances. Another lesser-known aspect of corticotropic deficiency is its involvement in the pathogenesis of cognitive impairment, particularly concentration difficulties [41, 42]. These symptoms strongly resemble those described in long COVID syndrome [43].

When discussing the influence of corticosteroid therapy, a higher proportion of patients in G1 had been hospitalized (G1: 59.3% vs G2: 28.1%), which explains the higher prevalence of corticosteroid use in this group (G1: 50% vs G2: 21.8%). However, corticotropic deficiencies were more frequent in G2 ($P = .02$), and only one corticotropic-deficient patient had previously received corticosteroid therapy. This finding is supported by previous research indicating that glucocorticoids were not associated with central adrenal insufficiencies [6, 16, 44].

In our study, nearly 45% of patients exhibited severe GHD, with the majority of these deficiencies being observed in COVID-19 long-haulers. However, the levels of IGF-1 were comparable in both groups. A decrease in IGF-1 is highly suggestive of GHD, especially when other anterior pituitary axes are affected [24]. Our study carefully examined the baseline characteristics of both groups. Factors such as age, sex, BMI, and other baseline characteristics can influence GH secretion and testing outcomes. However, as mentioned in all primary results, there were no differences between baseline characteristics between the 2 groups. The 2 groups exhibit heterogeneity mainly in the severity of COVID-19 infection. Also, the diagnostic criteria and methodologies employed in our study were chosen based on established guidelines [23, 24]. Variations in diagnostic approaches across studies could influence the reported prevalence of GHD based on selected cutoff and immune assay kits. A lower GH cutoff used may demonstrate a higher prevalence of GHD. Biochemical criteria for the diagnosis of GHD are complicated by the lack of normative data that are age, sex, and BMI adjusted; by assay variability; and by the stimulus used [24]. With polyclonal radioimmunoassay, the cutoff values for stimulated GH levels for diagnosing GHD were established at levels between 3 and 5 ng/L [45]. Whether lower cutoffs should be used with the newer, more sensitive, 2-site assays has not been definitively determined. According to newer studies, which used a sensitive, immunochemiluminescent, 2-site assay, the values of 5.1 μg/L for the ITT and 4.1 μg/L for the GH-releasing hormone–arginine test had sufficient specificity and sensitivity for the diagnosis of GHD [46].

In nearly 40% of adult GHD cases, IGF-1 levels are either normal or at the lower limit of normal. This discrepancy can be explained by various associated factors that regulate IGF-1 secretion [47]. Thus, a low IGF-1 level is not necessary for the diagnosis of GHD in adults [24].

To explain variation between both groups, obesity affects GH and IGF-1 secretions [48]. One of the caveats in interpreting the results of GH stimulation tests is that adult GHD itself is complicated by an increased susceptibility to central obesity. Obesity per se is a state of relative GHD, and earlier physiologic studies in obese individuals have shown that spontaneous GH secretion is reduced [49], GH clearance is enhanced, and stimulated GH secretion is reduced. Conversely, serum IGF-I levels are unaffected, or even increased, and this discordance is related to the increased hepatic GH responsiveness. The decreased serum GH levels in obesity upregulate GH receptor and sensitivity. While obesity is generally associated with higher levels of IGF-1, it is important to note that not all IGF-1 may be biologically active. Obesity can lead to changes in the levels of IGF-1 binding proteins (IGFBPs), which can affect the bioavailability of IGF-1. Some IGFBPs may sequester IGF-1, reducing its availability for binding to receptors and exerting its growth-promoting effects [50].

GHD typically presents with generalized fatigue and is also associated with cognitive impairment, decreased muscle strength, and altered physical condition [51, 52]. These manifestations significantly affect quality of life and could account for some of the symptoms observed in COVID-19 long-haulers [45].

The majority of patients in both groups in our study were vaccinated against COVID-19. In a pilot literature review conducted by our team regarding pituitary-related complications associated with this vaccination, only 5 cases of hypophysitis and 3 cases of pituitary apoplexy were reported [53, 54]. Furthermore, the absence of vaccination is considered a risk factor for long COVID [55]. Therefore, its involvement in antehypophyseal deficits in our study is unlikely.

To the best of our knowledge, this is the first prospective study to compare the antehypophyseal hormonal profile of patients recovered from COVID-19 and patients experiencing long COVID on the African continent. It is also the first study in the world to evaluate, in this context, the corticotroph and somatotroph axes in such a large group of patients using the ITT.

Indeed, the ITT remains the gold standard for evaluating the corticotroph and somatotroph axes [23, 24]. Most studies evaluating the corticotroph axis have used the Synacthen test (ST) [28]. The consensus of the French Society of Endocrinology emphasizes that the ST can yield falsely normal results in cases of recent corticotroph insufficiency or partial corticotroph insufficiency [56]. The relevance of studies that assessed the corticotroph axis in COVID-19–recovered patients using the ST after only a few weeks is therefore questionable. It is likely that partial corticotroph deficiencies may have gone unnoticed in these studies.

Our study extends over a relatively long postinfection evaluation and follow-up period (G1: 11.5 months and G2: 11 months) compared to other studies that have examined postinfectious cases for only a few weeks.

However, the most important aspect of our study is the confirmation that patients with post–COVID-19 syndrome are more likely to have anterior pituitary hormone deficiencies. These deficiencies certainly play a role in the pathophysiology of some long COVID symptoms and the impairment of these patients' quality of life.

A limitation persists in all research on long COVID, as in our study: the absence of a precise and reproducible definition of the long COVID group. These patients could not be thoroughly explored because no consensus has been validated regarding the necessary investigations for the diagnosis of post–COVID-19 syndrome. Currently, there is no standardized test to diagnose long COVID. It is important to note there is no one or set of typical symptoms. The current differential diagnosis process is based on the framework put forward by WHO Delphi recommendations [14]. In most cases, this process involves a lengthy process of an additional

battery of tests, especially to rule out other conditions/diseases. As we mentioned in our study, all the patients underwent a battery of tests for their main symptoms and all results were normal.

Regarding our pathophysiological hypotheses, we can provide only assumptions about the exact cause of these deficiencies. Although the hypothesis of hypophysitis is the most likely, further evaluation through hypothalamo-hypophyseal imaging is necessary.

Conclusions

Our study has demonstrated that long COVID patients are more likely to have anterior pituitary hormone deficiencies. Our work is original as it is the only study that has analyzed anterior pituitary function in a substantial sample using an ITT. The endocrine hypothesis involving anterior pituitary insufficiency can be considered to explain post–COVID-19 syndrome. Further research similar to ours will be necessary to highlight the link between long COVID and anterior pituitary deficiencies. This will help modify the management of post–COVID-19 syndrome and establish new recommendations for its evaluation.

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Author Contributions

Dr Ben Hadj Slama Nassim and Dr A.C.H. Taieb drafted the manuscript. All authors helped in the patient care and read and approved the final manuscript.

Disclosures

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in "References."

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