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Use of testosterone replacement therapy to treat long-COVID-related hypogonadism

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Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can impair pituitary–gonadal axis and a higher prevalence of hypogonadism in post-coronavirus disease 2019 (COVID-19) patients compared with the general population has been highlighted. Here we report the first case of a patient affected with a long-COVID syndrome leading to hypogonadism and treated with testosterone replacement therapy (TRT) and its effects on clinical and quality of life (QoL) outcomes. We encountered a 62-year-old man who had been diagnosed with hypogonadotropic hypogonadism about 2 months after recovery from COVID-19 underwent a complete physical examination, general and hormonal blood tests, and self-reported questionnaires administration before and after starting TRT. Following the TRT, both serum testosterone level and hypogonadism-related symptoms were improved, but poor effects occurred on general and neuropsychiatric symptoms and QoL. Therefore, hypogonadism does not appear to be the cause of neurocognitive symptoms, but rather a part of the long-COVID syndrome; as a consequence, starting TRT can improve the hypogonadism-related symptoms without clear benefits on general clinical condition and QoL, which are probably related to the long-COVID itself. Longer follow-up might clarify whether post-COVID hypogonadism is a transient condition that can revert as the patient recovers from long-COVID syndrome.

Learning points

- Hypogonadism is more prevalent in post-COVID-19 patients compared with the general population.
- In these patients, hypogonadism may be part of long-COVID syndrome, and it is still unclear whether it is a transient condition or a permanent impairment of gonadal function.
- Testosterone replacement therapy has positive effects on hypogonadism-related clinic without clear benefits on general symptomatology and quality of life, which are more likely related to the long-COVID itself.

Background

According to the World Health Organization (WHO), post-coronavirus disease 2019 (COVID-19) condition (or long-COVID) occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday

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functioning. Symptoms might be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time (1). At least one-third of COVID-19 patients have been reported to suffer from post COVID-19 condition (2).

The influence of COVID-19 on pituitary–gonadal axis in the short and medium term and both hypogonadism and spermatogenesis disorders has been reported (3, 4). Notably, low serum testosterone levels have been associated to worse outcomes in COVID-19 patients (5).

Furthermore, several studies have also reported lower testosterone levels in post-COVID-19 patients after a few months from the recovery (4, 6). Some authors speculate that hypogonadism together with endothelial dysfunction, prolonged hypoxia due to respiratory impairment, and post-traumatic stress disorder can be responsible of the erectile dysfunction reported in many long-COVID patients (7).

To date, at the best of our knowledge, no case reports have been published about the use of testosterone replacement therapy (TRT) to treat long-COVID patients with hypogonadism. The aim of this work is to report a case of long-COVID patient with subsequent hypogonadism treated with TRT and its effects on clinical and quality of life (QoL) outcomes.

Case presentation

A 62-year-old man was admitted in March 2021 for SARS-CoV-2 interstitial pneumonia and treated with remdesivir, glucocorticoids, heparin, oxygen therapy, and continuous positive airway pressure (CPAP) with subsequent gradual weaning and discharge after about 1 month of hospitalization. About 2 months later, the patient reported appearance of gynecomastia, fatigue, joint pain, and gradual weight gain of 11 kg, but no major changes in libido and morning erections or erectile dysfunction.

Physical examination showed weight 82.9 kg, height 173 cm, BMI 27.7 kg/m^2, waist size 101.5 cm, and arm span 182 cm; he presented a normal virilization with Tanner stage V, bilateral testes volume, measured with Prader orchidometer, of 25 mL, and with a moderate increase in their consistency together with mild ectasis and tenderness of both the epididymides. Bilateral gynecomastia was also palpable and moderately painful.

Cardiopulmonary examination was uneventful.

His history revealed Hashimoto's thyroiditis with normal thyroid functionality; hypertension was treated with enalapril 20 mg; benign prostatic hyperplasia causing mild obstructive symptoms, untreated; mild bronchial asthma; and lung micronodules in follow-up. Moreover, in 2020, he had undergone surgery for melanoma with removal of axillary lymph nodes bilaterally.

Investigation

Given his clinical presentation, the patient underwent hormonal and general blood tests which revealed hypogonadotropic hypogonadism with total testosterone: 9.49 nmol/L (2.73 ng/mL, reference range (RR): 9.90–27.8 nmol/L), sex hormone binding globulin (SHBG): 27 nmol/L (RR: 10–70), calculated free testosterone (cFT): 198 pmol/L (RR: >220), luteinizing hormone (LH): 5.5 U/L (RR: 1.7–8.6), and follicle-stimulating hormone (FSH): 4.1 U/L (RR: 1.5–12.4) in an otherwise normal pituitary function. There was also evidence of impaired fasting glycaemia with blood glucose 113 mg/dL (6.27 nmol/L, RR: 70–100 mg/dL). Anti-GAD and anti-pituitary antibodies were negative (Table 1).

Due to the findings during physical examination, scrotal and breast ultrasound were performed: testicular and scrotal ultrasound showed no signs of phlogosis, but evidence of moderate hydrocele and grade I varicocele on

Table 1 Blood general and hormonal parameters at the time of presentation, during follow-up, and after 2 months of testosterone replacement therapy.

Parameters	At presentation	12-month FU	Post treatment
Total testosterone (nmol/L)	9.49	6.7	12.98
SHBG (nmol/L)	27	21	–
FcT (pmol/L)	198	152	–
Estradiol (pmol/L)	70	–	–
LH (U/L)	5.5	–	–
FSH (U/L)	4.1	–	–
TSH (mU/L)	1.93	3.2	–
fT4 (ng/dL)	–	1.1	–
fT3 (pg/mL)	–	3.75	–
PRL (µg/L)	9.2	8.6	–
ACTH (ng/L)	23.8	36.8	–
Cortisol (µg/dL)	9.84	18.8	–
IgF1 (µg/L)	–	106	–
FBC			
Hb (g/dL)	–	14.2	14.4
HCT (%)		42.8	41.6
AST/ALT (U/L)	18/19	–	17/25
Creatinine (mg/dL)	0.97	–	0.96
Blood glucose (mg/dL)	113	–	–
Anti-TPO/TG antibodies	+	–	–
Anti-pituitary antibodies	–	–	–
Total PSA (µg/L)	–	1.65	2

+, positive; –, negative; ACTH, adrenocorticotropic hormone; anti-TPO, anti-thyroid peroxidase; anti-TG, anti-thyroglobulin; AST/ALT, alanine aminotransferase and aspartate aminotransferase; fT3, free T3; fT4, free T4; fcT, free calculated testosterone; FBC, full blood count; FSH, follicle-stimulating hormone; Hb, hemoglobin; HCT, hematocrit; IgF1, insulin-like growth factor 1; LH, luteinizing hormone; PRL, prolactin; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin; TSH, thyroid-stimulating hormone.

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the left testicle emerged and breast ultrasound confirmed a moderate hypertrophy of mammary tissue. In view of the patient's history and in suspicion of a transient form of central hypogonadism, after appropriate discussion with the patient it was decided to follow up his clinical picture without starting any treatment.

Treatment

Nonetheless, after 12 months, the patient was presenting a worsening in his symptoms (severe asthenia, fatigue, mood change) and a new hormone evaluation showed an overt hypogonadism with total testosterone 6.7 nmol/L (1.93 ng/mL) and cFT 152 pmol/L (Table 1). Therefore, TRT was initiated with testosterone gel 2% 20 mg (two applications) applied topically once daily in the morning.

Outcome and follow-up

After 2 months of therapy, the patient was re-evaluated clinically and biochemically. Blood samples were collected about 3 h after gel application. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and The Arthritis Impact Measurement Scale (AIMS) were used to assess pain, stiffness, and physical functioning of the joints and social, psychological and physical components of patient's health status, respectively. QoL was evaluated by Short Form Health Survey 36 (SF-36), whereas International Index of Erectile Function Questionnaire – IIEF 5 and Androtest were used to assess erectile dysfunction and symptoms of hypogonadism (Table 2). At this specific follow-up time-point, a normalization of total testosterone to 12.98 nmol/L (3.74 ng/mL, Table 1) and an improvement in specific signs of hypogonadism (particularly a reduction of his gynecomastia) was observed, without, however, any significant reported benefits on general symptoms such as fatigue, deflected mood, joint and muscle pain, or QoL (Fig. 1). No major change in body weight was noticed.

Discussion

In the literature, we find evidence of higher prevalence of hypogonadism in COVID-19 patients both in short- and medium-term compared with the general population. Salonia *et al.* (6), after a 7-month follow-up, showed that testosterone levels increase with time since recovery, but a condition of hypogonadism remains in a large percentage of patients. Moreover, Moreno-Perez *et al.* (4) reported that long-COVID patients with low serum testosterone had a poorer QoL and physical functioning. Unfortunately, all these studies, as well as our clinical case, share the limitation of not having data on gonadal function prior to the diagnosis of COVID-19. The mechanisms responsible for this higher prevalence of hypogonadism in long-COVID patients are only partly known. Angiotensin-converting enzyme 2 (ACE2) receptor, crucial for viral cell entry, has been documented on both seminiferous tubules and Leydig cells and, consequently, SARS-CoV-2 can potentially impair testosterone and sperm production. In addition, the inflammatory response due to viral localization within the testis can induce the development of a local immune reaction, contributing to testicular damage (3). On the other hand, according to other authors, the absence of documented coexpression of ACE2 receptors

Table 2 Quesionnaires administrated.

Questionnaire	At diagnosis	Post TRT
WOMAC (total)	28	21
Pain	4	3
Stiffness	6	4
Physical functioning	18	14
AIMS (total)	96	88
Mobility	4	4
Physical activity	7	7
Dexterity	5	5
Household activity	7	7
Social activities	14	16
Activities of daily living	4	4
Pain	17	12
Depression	15	11
Anxiety	23	22
IIEF-5	25	25
ANDROTEST	15	20
SF 36	101	104

AIMS, The Arthritis Impact Measurement Scale; ANDROTEST; IIEF-5, International Index of Erectile Function Questionnaire; SF-36, Short Form Health Survey 36; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

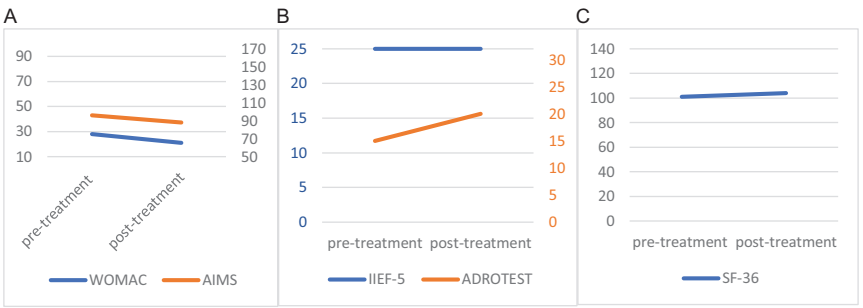

Figure 1

WOMAC and AIMS (A), IIEF-5 and Androtest (B), and SF-36 (C) scores pre-TRT and post TRT.

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and type II transmembrane serine protease (TMPRSS2), another necessary protein for the virus to enter the cell, in testis makes viral entry and infection unlikely (8). Other studies demonstrated a higher prevalence of hypogonadotropic forms rather than primary damage in hypogonadic patients in acute infection phase (4, 9): actually, the development of secondary hypogonadism is a frequent complication of several acute and chronic illnesses. Indeed, increased plasma levels of TNF-α, IL-1, and IL-6 have been observed in patients with COVID-19, especially in severe infection (10), and such cytokines are known to be related to an impairment of GnRH neurons in the hypothalamus (11, 12). This appears to be not so different from what has been reported in other conditions of low-grade inflammation, i.e. in metabolic syndrome (12), even though the exact mechanism underlying this association is not fully understood.

To our knowledge, there are no data on the effects of TRT in hypogonadal male patients in the acute phase of disease nor in long-COVID.

In our patient, benefits were evident on the specific signs and symptoms of hypogonadism, as evidenced by comparison of Androtest scores and reduction of gynecomastia after initiation of treatment and normalization of testosteronemia (Tables 1, 2 and Fig. 1B). Only partial benefits can be seen, however, on nonspecific symptoms such as fatigue and depression and musculoskeletal symptoms (Table 2 and Fig. 1A). Overall, no improvement in QoL was appreciated by the patient nor did it emerge from the SF-36 questionnaire administered (Table 2 and Fig. 1C).

Moreover, in the light of our experience and of what has been reported in the literature, it is conceivable that the neuropsychiatric symptoms such as depression and anxiety are related more to the long-COVID condition than to the hypogonadal state, since the benefit of TRT on these parameters was only partial. Moreover, it is not known how much this improvement is related to the restoration of eugonadism or simply to a progressive resolution of the long-COVID syndrome over time.

Finally, due to the potential reversibility of this condition, it is worth considering a discontinuation of TRT, especially once a recovery from long-COVID symptoms occurs, and a periodical revaluation of the gonadal function of the subject to confirm a potential restoration of normal gonadal function.

Concluding, we report the effects of TRT in a patient affected with long COVID and presenting hypogonadotropic hypogonadism. The effects of the treatment on multiple validate scores seem to suggest that hypogonadism is part of the long-COVID syndrome and not the cause of neurocognitive symptoms, and that initiation of TRT can improve the hypogonadism-related specific symptoms without clear benefits on general ones and QoL, which are more likely related to the long-COVID itself. Longer follow-up might clarify whether hypogonadism in these patients is a transient condition that can revert as the patient recovers from long-COVID syndrome and after proper post-COVID rehabilitation, if necessary.

Declaration of interest
The authors declare that they have no competing interests. Marco Bonomi is on the editorial board of *Endocrinology, Diabetes & Metabolism Case Reports*. He was not involved in the review or editorial process for this paper, on which he is listed as an author.

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Patient consent
Written informed consent for publication of their clinical details was obtained from the patient.

Author contribution statement
All authors participated in the diagnosis and management of this patient and AA and BC also in manuscript submission. All authors reviewed and approved the final draft.

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