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Metformin for fatigue and cognitive dysfunction associated with postCOVID-19 condition and other suspected mitochondrial dysfunction: a case series

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Case Report

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Abstract

Background

PostCOVID-19 condition (long COVID) is commonly associated with persistent fatigue and cognitive dysfunction. This and other similar syndromes seem to involve immunologic, metabolic and neurologic causes. Evidence-based therapies remain limited.

Case presentation:

We report three women with severe fatigue and cognitive dysfunction (two following COVID-19 and one temporally associated with aromatase inhibitor therapy) in whom metformin was associated with rapid, clinically meaningful improvement. In each case, symptoms recurred on metformin discontinuation and improved again after re-initiation.

Conclusions

These observations support further evaluation of metformin for fatigue and cognitive dysfunction in selected patients with post-viral syndromes or suspected mitochondrial impairment.

Background

Post–COVID-19 condition (long COVID) is a heterogeneous syndrome that commonly includes persistent fatigue, cognitive dysfunction (“brain fog”), post-exertional symptom exacerbation, sleep disturbance and dysautonomia. Similar symptom clusters occur in other post-infectious syndromes, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[1,2] Evidence-based therapies remain limited and management is often supportive.

Metformin is a biguanide used widely for type 2 diabetes.[3] derived from *Galega officinalis* (goat’s rue) and has been used clinically for decades[3,4]. Beyond lowering glucose, it modulates immune-metabolic pathways, including AMPK signaling and mitochondrial bioenergetics, providing biological plausibility for benefit in disorders characterized by altered bioenergetics and/or immune dysfunction.[5,6]

However, clinical trials have reported mixed results and the role of metformin in established long COVID, or in other settings of suspected mitochondrial dysfunction, remains uncertain[8,9]. We describe three patients in whom metformin use was temporally associated with rapid and clinically meaningful improvement in fatigue and cognitive dysfunction.

Patient 1

A 50-year-old Caucasian woman developed acute chest pain and dyspnea in early 2021 while at work. Emergency department assessment did not identify acute cardiac disease. SARS-CoV-2 testing was not performed at symptom onset; a test obtained several days later was negative. She was unvaccinated at the time because of reported allergies

Over subsequent weeks she developed persistent dyspnea, myalgias, upper back pain, resting tachycardia (~ 110 beats/min) and profound fatigue. Pulmonary function tests were normal. In August 2021 she was evaluated at a tertiary unexplained dyspnea clinic and diagnosed with post–COVID-19 cardio-neuropathy with preload deficiency; this was later supported by cardiac positron emission tomography (November 2021). Management included melatonin, physical therapy, pyridostigmine, saline infusions, compression stockings and work-hour restrictions.

Autonomic testing later demonstrated reduced sweating consistent with non–length-dependent small fiber/sudomotor neuropathy, without orthostatic hypotension or orthostatic tachycardia. Despite multidisciplinary management, fatigue and cognitive dysfunction persisted and substantially limited daily function. In mid-2025, following an upper respiratory infection, she reported worsening fatigue and cognitive symptoms. Given concern for mitochondrial dysfunction contributing to symptom exacerbation, extended-release metformin 500 mg once daily was started. Within 1 week she reported marked improvement in energy and cognitive clarity, without gastrointestinal adverse effects or hypoglycemia. When metformin was stopped, symptoms partially recurred; re-initiation was again associated with improvement.

Patient 2

A 60-year-old Caucasian woman had a severe COVID-19 infection in late 2020 and subsequently developed persistent and progressive symptoms including fatigue, cognitive dysfunction, headaches, impaired thermoregulation, peripheral neuropathy, intermittent abdominal pain, chest pain and recurrent oral and cutaneous lesions

She was found to have vitamin B12 deficiency and markedly low morning cortisol and underwent evaluation for hypothalamic–pituitary–adrenal axis dysfunction. In April 2023 she was admitted with chest pain, confusion and hypertensive urgency. Extensive inpatient investigations did not reveal a unifying diagnosis, and she was discharged with continuing symptoms. She was declined evaluation at the local post–COVID-19 clinic. A trial of metformin was started and titrated to 1500 mg daily over approximately 2 weeks.

Within 10–14 days of reaching 1500 mg/day she reported improvement in fatigue, cognitive dysfunction, thermoregulation and mucocutaneous lesions. By 6 weeks, cognitive symptoms had resolved. Attempts to taper metformin every few months were followed by recurrence of fatigue and cognitive symptoms. After ~ 18 months of therapy she tapered and discontinued metformin over 4 weeks without relapse. Residual peripheral neuropathy persisted, but she otherwise returned to baseline functioning.

Patient 3

A 50-year-old Caucasian woman with a history of ovarian cancer (status post hysterectomy) developed severe fatigue and cognitive dysfunction while receiving letrozole. Symptoms were refractory to non-pharmacological interventions (yoga, acupuncture and qigong) and substantially impaired quality of life. Given concern for medication-associated mitochondrial dysfunction related to estrogen depletion, metformin was started. Within 48 hours she reported complete resolution of fatigue and cognitive symptoms, which was sustained on follow-up. When metformin was stopped, symptoms recurred and resolved again on re-initiation.

Investigations were heterogeneous and reflected each patient's presenting features. Patient 1 had normal pulmonary function testing; subsequent evaluation at a tertiary dyspnea clinic supported a diagnosis of cardio-neuropathy with preload deficiency and cardiac positron emission tomography was supportive. Autonomic testing later demonstrated reduced sweating consistent with small fiber/sudomotor neuropathy without orthostatic hypotension or orthostatic tachycardia. Patient 2 was found to have vitamin B12 deficiency and low morning cortisol and underwent extensive inpatient evaluation during an admission for chest pain, confusion and hypertensive urgency without identification of a unifying diagnosis. For Patient 3, symptoms occurred during aromatase inhibitor therapy; specific investigations are not reported.

Discussion

The differential diagnosis for persistent fatigue and cognitive dysfunction is broad and includes post–COVID-19 condition, ME/CFS,[1,2] dysautonomia (including small fiber neuropathy), sleep disorders, endocrine disorders (including adrenal insufficiency and thyroid disease), nutritional deficiency (including vitamin B12 deficiency), medication effects, mood disorders and cardiopulmonary disease. In these cases, clinical history and systematic elimination of other diagnoses by prior evaluations supported post-viral or medication-associated syndromes with a suspected mitochondrial/immune-metabolic cause.

In all three patients, metformin was initiated as an empiric trial for severe fatigue and cognitive dysfunction in the setting of suspected mitochondrial dysfunction. Patient 1 received metformin extended release 500 mg once daily. Patient 2 was titrated to 1500 mg daily over approximately 2 weeks. Patient 3 received metformin extended release 500 mg once daily. In Patient 1, concurrent management included melatonin, physical therapy, pyridostigmine, saline infusions, compression stockings and work-hour restrictions.

All three patients reported rapid and clinically meaningful improvement in fatigue and cognitive dysfunction after starting metformin (within 48 hours to ~ 2 weeks). Patient 1 reported no gastrointestinal adverse effects or hypoglycemia. In all patients, symptoms recurred after stopping metformin and improved again after re-initiation. Patient 2 experienced recurrence of fatigue and

cognitive symptoms with repeated taper attempts over months; after ~ 18 months she discontinued metformin over 4 weeks without relapse, though residual peripheral neuropathy persisted.

This case series describes three women with severe fatigue and cognitive dysfunction in whom metformin use was temporally associated with rapid improvement. Two patients had symptoms following COVID-19 and one had symptoms temporally associated with aromatase inhibitor therapy. In all cases, symptom recurrence on metformin withdrawal with improvement on re-challenge supports a potential treatment signal, although causality cannot be established.

Metformin's immune-metabolic effects provide a biologically plausible reason that it may benefit syndromes characterized by impaired energy availability or immune activation.[5,6] Metformin activates AMPK and influences mitochondrial bioenergetics and redox signaling, and it may modulate inflammatory pathways including the NLRP3 inflammasome.[6,7] These effects have led to interest in metformin as a repurposed therapy beyond diabetes.

Post–COVID-19 condition overlaps clinically with other post-infectious syndromes such as ME/CFS,[1,2] and mechanistic heterogeneity is likely (including immune dysregulation, autonomic dysfunction and altered energy metabolism). Therapies that modify immune-metabolic signaling, such as metformin, could be helpful for selected patients. However, patient selection criteria and optimal dosing and duration remain unknown.

Randomized trial data relevant to metformin in COVID-19–associated outcomes are mixed. In one large randomized-controlled outpatient COVID-19 treatment trial, metformin use was associated with a lower incidence of long COVID during follow-up. This study used clinician-based diagnosis as selection criteria.[8] In contrast, a subsequent trial using a narrower definition of post-acute sequelae did not demonstrate benefit over placebo.[9] Differences in case definitions, timing of treatment initiation and duration may contribute to these discrepant results; notably, both trials used relatively short treatment courses and the latter narrow, though easily measured, disease definition. This latter may have resulted in more specificity than sensitivity in identifying responsive cases.

The observations in patients 1 and 2 raise the possibility that longer exposure may be relevant in chronic symptom states, but this series cannot determine optimal dose, duration or discontinuation strategy.

Limitations This report describes three cases without a control group; causality cannot be inferred. Outcomes were patient-reported rather than measured with validated instruments, and spontaneous improvement or regression to the mean cannot be excluded. Concurrent therapies and natural variation in the course of disease may also have contributed. Nonetheless, consistency of response across different clinical contexts, rapidity of response in two patients and symptom recurrence on withdrawal in all cases support further study.

Conclusions

In three women with severe fatigue and cognitive dysfunction (two following COVID-19 and one temporally associated with aromatase inhibitor therapy), metformin use was temporally associated with rapid symptomatic improvement and reproducible symptom recurrence on withdrawal with improvement on re-challenge. Although causality cannot be inferred from an uncontrolled case series, these cases support hypothesis generation and motivate prospective studies using standardized outcome measures and mechanism-informed patient selection.

Declarations

Patient perspective

Patient 3: “I have my life back. I can think again.”

Consent

Written informed consent for publication was obtained from all patients.

Ethics approval and consent to participate: IRB approval not needed for case reports by our IRB. Case reports involving one, two, or three patients are generally considered medical or educational activities, not "research" as defined by federal regulations (45 CFR 46).

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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