Orthostatic intolerance (OI) is a cardiovascular autonomic disorder defined as having difficulty tolerating the upright posture because of symptoms that abate when returned to supine. The common forms of OI include orthostatic hypotension (both neurogenic and nonneurogenic), vasovagal syncope, and postural tachycardia syndrome (POTS). Chronic orthostatic intolerance, present for at least 3 months, although symptoms may wax and wane, has been recorded in a significant proportion of patients with long COVID. In this study, Japanese authors investigated the prevalence of a positive standing test (ST) and related autonomic manifestations in patients diagnosed with long COVID syndrome.

The central nervous system (CNS) symptoms of OI are related to reduced brain perfusion during orthostatic stress. Loss of consciousness or a sense of impending loss of consciousness, cognitive deficits (memory loss and decreased reasoning and concentration), dizziness or lightheadedness, headache, exhaustion, orthostatic hypotension, and occasionally hypertension, weakness, nausea, abdominal pain, sweating, tremulousness, and intolerance to exercise are typical symptoms. Orthostatic intolerance is common in pediatrics. Approximately 40% of people faint during their lives, half faint during adolescence, and the peak age for first fainting is 15 years.

Neurogenic orthostatic hypotension is caused by autonomic failure attributable to inadequate release of norepinephrine from sympathetic vasomotor neurons, leading to vasoconstrictor failure. Autonomic failure can be primary, caused by preganglionic, postganglionic, or both forms of sympathetic failure; it can be genetic, as in dopamine beta-hydroxylase deficiency; autoimmune, or acquired as a secondary aspect of systemic disease. (Stewart JM. Mechanisms of sympathetic regulation in orthostatic intolerance. J Appl Physiol 113: 1659–1668, 2012.)
https://journals.physiology.org/doi/full/10.1152/japplphysiol.00266.2012

Evidence of partial autonomic denervation in some patients with POTS and preceding viral syndrome supports an underlying immune system-related cause. This is further supported by the detection of autoantibodies that cross-react with a wide range of cardiac proteins and α- and β-adrenergic receptors. Stewart JM, et al. Pediatric Writing Group of the American Autonomic Society. Pediatric Disorders of Orthostatic Intolerance. Pediatrics. 2018 Jan;141(1):e20171673. https://pmc.ncbi.nlm.nih.gov/articles/PMC5744271/

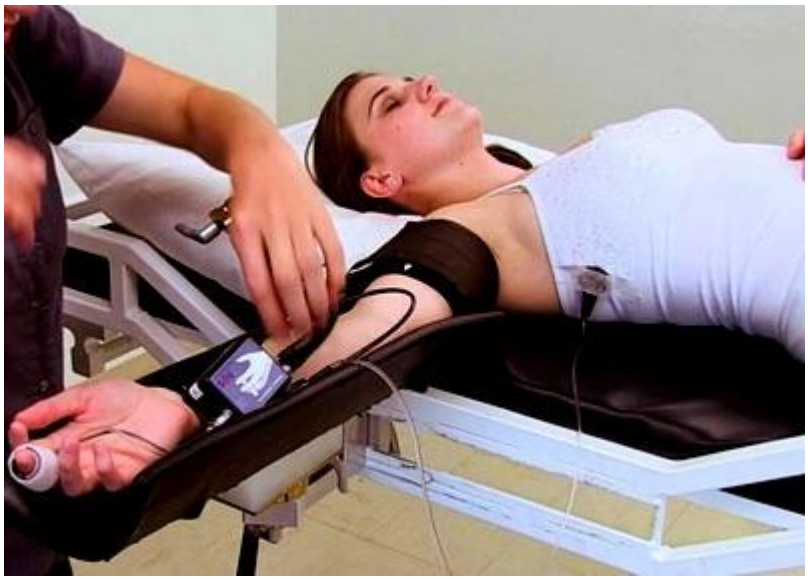
Notably, the study of Yapici-Eser et al. (2021), which investigated a mimicry between human proteins and SARS-CoV-2 proteins using a computational methodology, showed that SARS-CoV-2 proteins mimic 5 proteins linked with the α-adrenergic receptor signaling pathway, 9

proteins linked with the β1-adrenergic receptor signaling pathway, 9 proteins with the β2-adrenergic signaling pathway, and 6 proteins with the β3-adrenergic receptor signaling pathway. (Yapici-Eser H et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein Interactions. Front. Hum. Neurosci, 23 March 2021.) https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full Additionally, an immunohistochemical analysis of endocrine organ samples (pituitary, thyroid, and adrenal gland), taken at autopsy from individuals with *antemortem* SARS-CoV-2 infection, revealed abundantly expressed SARS-CoV-2 proteins in the cells of the adenohypophysis. In contrast, the cells of the neurohypophysis did not express viral proteins. Computational methods showed that human coronaviruses share 117 immune pentapeptide epitopes with 18 autoantigens expressed by human endocrinocytes. (Kolobov VE et al. Post-COVID Endocrine Disorders: Putative Role of Molecular Mimicry and Some Pathomorphological Correlates. Diagnostics 2023, 13, 522.) https://doi.org/10.3390/diagnostics13030522 Interestingly, individuals with post-COVID-19 vaccination syndrome were found to have higher levels of autoantibodies against six receptors involved in autonomic regulation, including the angiotensin II type 1 receptor, endothelin-1 type A receptor, M2 and M3 muscarinic acetylcholine receptors, β2 adrenergic receptor, and MAS1 receptor. https://discovermednews.com/autoantibodies-against-elements-of-autonomic-regulation-post-covid-vaccination-syndrome/

The secretion of growth hormone (GH), like other anterior pituitary hormones, is regulated through a complex neuroendocrine control system that comprises two main hypothalamic regulators: growth hormone-releasing hormone (GHRH), which stimulates GH synthesis and secretion to a large extent, and somatostatin, which inhibits GH secretion from the anterior hypophysis. Extensive pharmacologic studies in man and animals indicate a stimulatory effect of central norepinephrine and dopamine on GH secretion. Stimulation of CNS α-adrenergic receptors elicits GH release in men. (Terry LC, et al. Regulation of episodic growth hormone secretion by the central epinephrine system. Studies in the chronically cannulated rat. J Clin Invest. 1982; 69(1): 104-12.) https://pmc.ncbi.nlm.nih.gov/articles/PMC371173/

Previous studies have investigated the relationship between GH levels and the occurrence of POTS. Johansson et al. (2021) found lower median plasma GH levels and higher supine heart rates (HR) and diastolic blood pressures (but not systolic blood pressures) in patients with POTS than in control subjects. (Johansson M et al. Circulating levels of growth hormone in

postural orthostatic tachycardia syndrome. Scientific Reports 2021; 11:8575). https://doi.org/10.1038/s41598-021-87983-5 In contrast, a study that used a proteomics approach reported elevated GH plasma levels in patients with POTS. (Medic Spahic, J. et al. Proteomic analysis reveals sex-specific biomarker signatures in postural orthostatic tachycardia syndrome. BMC Cardiovasc. Disord. (2020) 20, 190.) https://doi.org/10.1186/s12872-020-01465-6



***About the study***

The study was conducted in outpatients diagnosed with long COVID syndrome, which lasts for more than one month. The majority of patients were infected during the Omicron phase (70%). Due to the symptoms of OI, such as palpitation and syncope, the patients had undergone a standing test (ST). They had not received any drug for long COVID treatment.

49% of participants in the ST-positive group, and 64% in the ST-negative group received at least 2 doses of COVID-19 vaccines.

Information on age, gender, body mass index, smoking/alcohol drinking habits, severity of the acute phase of COVID-19, viral variants, history of COVID vaccination, clinical symptoms of long COVID, and results of ST were obtained from medical records.

In the active standing test, an individual lies supine for 5 minutes during which time their baseline blood pressure and heart rate (HR) are measured, and then stands up actively for

10 minutes. The monitoring of systolic and diastolic blood pressures and HR is conducted every two minutes for up to 10 minutes in a standing position. Symptoms such as fatigue, nausea, lightheadedness, shortness of breath, headache, pain, and impaired concentration are recorded while the individuals are supine and standing. The increase in HR from the basal HR of 30 beats per minute (bpm) or more, the increase to 120 bpm or more over the same period, and the decrease in systolic blood pressure of 25 mmHg or more are all considered positive indicators for the ST.

***Results***

The most frequent daily symptoms in long COVID patients were fatigue, headache, sleep disturbance, dizziness, dyspnea, nausea, and poor concentration.

***A standing test (ST)***

38% (33/86) of patients with long COVID were positive for ST. They were significantly younger than the ST-negative patients (median age was 20 years *vs.* 40 years). Furthermore, 49% of long COVID patients positive for ST were under 20 years of age, while the proportion of patients under 20 years of age in the ST-negative group was only 21%. There was no significant difference in the gender ratio between the ST-positive and ST-negative groups.

Both ST-positive and ST-negative patients with long COVID experienced a significant increase in HR after standing up from the supine position. However, the initial increment in HR in the ST-positive patients was twice as high (25 bpm) as in the ST-negative patients (14 bpm). Also, the ST-positive patients with long COVID showed a greater initial increase in HR during ten minutes after standing up than the ST-negative patients.

Both groups had a moderate increase in systolic and diastolic blood pressures. The increase in systolic blood pressure 5 minutes after standing up compared to the baseline value did not differ between the two groups. However, diastolic blood pressure immediately after standing up was higher in the ST-positive group (+14 mmHg) than in the ST-negative group (+9 mmHg), suggesting that an acute rise in diastolic blood pressure immediately after standing up is characteristic of patients with long COVID positive for ST. The authors emphasized that this phenomenon of an initial increase in diastolic blood pressure was also

found in a previous study conducted in POTS patients, unrelated to COVID.

There were no significant differences in the clinical symptoms between the ST-positive and ST-negative groups with long COVID. In ST-positive patients, there was an insignificant tendency for accompanying symptoms, such as nausea and tachycardia.

The ST-positive patients and ST-negative patients did not differ in body mass index, smoking and drinking, the severity of COVID-19, viral variants, vaccination history, peripheral blood counts, and biochemical data on liver and kidney function, electrolytes, and inflammatory factors.

### *Laboratory parameters*

Since the ST-positive group with long COVID included a large proportion of younger patients, the groups were divided into two age groups: under 20 years and 20 years or older. There was no significant difference in thyroid hormones (free thyroxine (FT4), thyrotropin (TSH), and the ratio of TSH/FT4) or adrenocortical hormones (cortisol, adrenocorticotropin (ACTH), and the ratio of ACTH/cortisol) between the ST-positive and ST-negative patients with long COVID, under 20 years of age.

However, patients with long COVID positive for ST under 20 years of age had lower serum growth hormone levels than the ST-negative group of the same age. These findings are consistent with the aforementioned study, which found lower plasma GH levels and higher diastolic blood pressure (but not systolic blood pressure) in POTS patients, unrelated to COVID.

In patients with long COVID positive for ST, aged 20 years or older, serum cortisol levels were higher than in the ST-negative group of the same age.

### *Conclusion*

This study showed a high rate (38%) of positive standing tests in patients with long COVID and symptoms of orthostatic intolerance. Patients with long COVID positive for ST had an acute increase in diastolic blood pressure with increasing HR during active standing.

Patients with long COVID positive for ST were significantly younger than the ST-negative patients, and 49% of them were under 20 years of age. Patients with long COVID positive

for ST under 20 years of age had decreased circulating growth hormone levels. This was not the case in the ST-positive long COVID group aged 20 years or older, who were found to have elevated cortisol levels.

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### *Journal Reference*

Kato, A., Tokumasu, K., Yamamoto, K. *et al.* Clinical and endocrine features of orthostatic intolerance detected in patients with long COVID. *Sci Rep* 14, 17025 (2024). https://www.nature.com/articles/s41598-024-67815-y