



SARS-CoV-2 Omicron symptoms and adverse effects of GLP-1 RA therapy

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COVID-19 pandemic highlighted the increased risk for severe illness, hospitalization, and death related to obesity. Furthermore, COVID-19 infection risk appears to be associated with obesity [1]. In June 2021, US Food and Drug Administration approved once-weekly GLP-1 receptor agonist (RA) therapy semaglutide 2.4 mg for chronic weight management, followed by a recent approval from the European Medicinal Agency. The approvals were based on the results from the STEP phase 3a clinical trial program [2, 3], demonstrating clinically relevant average weight loss of up to 17–18% sustainable over 68 weeks, that is about twice as much compared with previous anti-obesity medications [2–4]. The therapy is safe and generally well tolerated with the most common adverse events being gastrointestinal. Nausea, diarrhoea, vomiting, and constipation are the most frequently reported events and occur in 74.2% participants receiving semaglutide compared to 47.9% of those receiving placebo [2]. The STEP 3 trial reports the median time of nausea 5 days, of vomiting 2 days, of diarrhoea 3 days and of constipation 27 days, occurring at any time during the treatment [3].

In our clinic, we currently follow 96 obese individuals (80 female, 16 male, age 48.3 ± 10.5 years, BMI 33.2 ± 1.5 kg/m²) treated with semaglutide. The average weight loss was 8.6 ± 3.1 kg over a 3-month treatment period with an average dose of 1.3 mg. Almost 85% of subjects reported loss

of appetite: 40% of them nausea, 3% vomiting and 25% obstipation.

On January the 17th, 2022, a 38-year-old woman contacted us because of a recent loss of appetite and sudden severe nausea and vomiting. She was treated with semaglutide for 3 months, titrated by standard escalation protocol, currently on a stable dose of 1 mg for the last 3, 5 weeks. She lost 9 kg from the time of the first administration and until that day did not reported any significant adverse effects. As she thought that the recent symptoms were related to the drug, she asked whether the next injection scheduled in 2 days should be postponed. In the following 2 days, 2 more women consulted us for severe nausea and loss of appetite, both being on a stable dose of semaglutide 1.0 mg for 3 weeks, one of them experiencing intermittent mild nausea previously. At the same time period, at week 12 of the standard titration protocol, the frequency of nausea significantly decreased and was reported in only about 10% of patients from our cohort.

On November 26, 2021, the World Health Organization designated the Omicron variant of SARS-CoV-2, as a variant of concern ([https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern)). On January 2, 2022, the UK Zoe COVID Study, designed to inform and plan response to the rapidly changing pandemic, updated the list of COVID Omicron symptoms [5]. Two frequent symptoms related to Omicron, nausea and loss of appetite, have been identified as possible stand-alone symptoms. While gastrointestinal symptoms were anecdotally associated with previous variants of the SARS-CoV-2 virus in adult population, they were never reported as frequent or standalone. Moreover, loss of appetite and nausea were recognized as more frequent Omicron-related symptoms in those who received double vaccination with or without the booster.

All 3 women were confirmed positive for SARS-CoV-2 by RT-PCR on the following day. PCR positive nasal swabs were sequenced for entire viral RNA using NGS sequencing

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approach (Illumina Novaseq 6000 with standard reagent kith) and Omicron variant was confirmed. One of them received two vaccinations with Comirnaty vaccine in January and February 2021, and had confirmed COVID-19 infection in September 2021, when the SARS-CoV-2 Delta represented more than 97% of all positive samples in our country. The other two received the 3rd dose of Comirnaty vaccine in November 2021. Other symptoms related to the infection occurred two days after the loss of appetite and nausea. Two women experienced mild headache, congestion and runny nose, one of them also a mild fever, whereas the one previously infected with SARS-CoV-2 did not develop any other symptoms except for mild tiredness. Loss of appetite and acute nausea disappeared within 48–72 h in all three cases. No other women from our cohort treated with semaglutide 1.0 mg for 2–3 weeks reported nausea or vomiting at that time.

This report aims to raise awareness among clinicians that the two frequently identified symptoms associated with SARS-CoV-2 Omicron infection mimic frequent side effect in individuals using GLP-1 RA. Loss of appetite and nausea could be attributed to the GLP-1 therapy and the SARS-CoV-2 infection overlooked particularly in those vaccinated two or three times. Individuals on GLP-1 RA therapy who experience loss of appetite and nausea at any time of the treatment trajectory, are currently advised to isolate and test themselves for potential SARS-CoV-2 infection.

Author contributions M.J. and A.J. conceived the report and wrote the manuscript. T.B. critically reviewed the manuscript and contributed to the final version. A.J. is the guarantor of this work and, as such, had full access to all the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the published version.

Declarations

Conflict of interest M.J. has given lectures, received honoraria, participated in conferences and advisory boards sponsored by pharmaceu-

tical companies including Amgen, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Novartis and Servier. A.J. has served as a consultant and is on Speakers Bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MerckSharp & Dohme (MSD), Novo Nordisk, Medtronic and Sanofi. None of the above had any role in this article, which has been written independently, without any financial or professional help, and reflects only the authors' opinion, without any role of the industry. T.B. is supported in part by the Slovenian Research Agency grant # P3-0343. No potential conflicts of interest relevant to this article were reported.

Human and animal rights Our study has been reviewed by the national ethics committee and has been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Informed consent All persons gave their informed consent prior to their inclusion in the study.

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