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RESEARCH LETTER

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The effect of semaglutide on intestinal iron absorption in patients with type 2 diabetes mellitus—A pilot study

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1 | BACKGROUND

Type 2 diabetes mellitus (T2DM) affects over 537 million individuals worldwide, posing a significant public health challenge.[1] Advances in pharmacological management have introduced glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as effective agents for glycemic control and weight reduction.[2] Emerging evidence suggests that newer therapies for managing T2DM, such as GLP-1 RAs, may influence the risk of anaemia.[3] Semaglutide, a long-acting GLP-1 RA, has demonstrated potent effects on glucose metabolism, appetite regulation and gastrointestinal motility.[4,5] Given its impact on gastric emptying, semaglutide may alter nutrient absorption, including iron, an essential micronutrient required for erythropoiesis and overall metabolic health.[6] The specific impact of semaglutide on iron absorption, especially concerning delayed gastric emptying, remains unexplored. This research aimed to investigate whether semaglutide affects iron absorption in patients with T2DM.

2 | METHODS

A prospective, single-centre study was conducted at University Hospital Dubrava, Zagreb, Croatia, between November 2023 and April 2024. Ethical approval was obtained and all participants provided written informed consent. The study was registered (Clinical Trial ID: NCT06629688).

The study enrolled patients with poorly controlled T2DM (HbA1c ≥7%) who began semaglutide therapy. Exclusion criteria included prior GLP-1 RA use, type 1 diabetes, iron deficiency anaemia, hemochromatosis, severe chronic illnesses, malignant neoplasms, infectious diseases, chronic rheumatic inflammatory diseases, malabsorption syndrome, inflammatory bowel disease, a history of gastrointestinal tract reduction surgery and the use of medications that interfere with iron absorption.[7]

The dosage of semaglutide was gradually increased from 0.25 mg to 1 mg every 4 weeks, followed by a maintenance dosage of 1 mg in all participants for an additional 2 weeks. An oral iron absorption test (OIAT) was conducted in an outpatient setting at both baseline and 10 weeks of semaglutide therapy.[8,9] OIAT involved administering a single 350 mg ferrous fumarate capsule (115 mg elemental iron) following a 12-h fast.[8,9] Venous blood samples were collected at baseline and 2 h after capsule ingestion. The blood samples were analysed to assess the complete blood count and parameters related to iron metabolism, including iron and ferritin concentration, unsaturated iron-binding capacity (UIBC) and total iron-binding capacity (TIBC). Transferrin saturation (TSAT) was calculated using the formula: (iron concentration / TIBC) × 100. OIAT adequacy was defined by a rise in iron concentration from a baseline of >17.9 μmol/L.[8–10] A clinically

TABLE 1 The dynamics of iron metabolism parameters in the OIAT before and 10 weeks after semaglutide administration in T2DM subjects, represented as the ratio of post-test (shown as number 2) to pre-test (shown as number 1) measurements for iron absorption.

Parameter	Baseline ($N = 51$)	Week 10 ($N = 51$)	p-value
Iron2/Iron1	1.19 (1.07–1.38)	1.08 (1–1.17)	0.001*
UIBC2/UIBC1	0.96 (0.9–1)	0.99 (0.95–1.02)	0.013*
TIBC2/TIBC1	1.02 (0.99–1.05)	1 (0.98–1.03)	0.143
TSAT2/TSAT1	1.17 (1.05–1.39)	1.07 (0.97–1.15)	0.001*
Feritin2/Feritin1	1.03 (1–1.06)	1.02 (0.99–1.06)	0.742
Adequate OIAT, *N* (%)	0/51 (0%)	1/51 (2%)	1.000

Note: Values are presented as median (IQR) unless otherwise specified.
Abbreviations: OIAT, oral iron absorption test; T2DM, type 2 diabetes mellitus; TIBC, total iron-binding capacity; TSAT, transferrin saturation; UIBC, unsaturated iron-binding capacity.
*Statistically significant at $p < 0.05$ level.

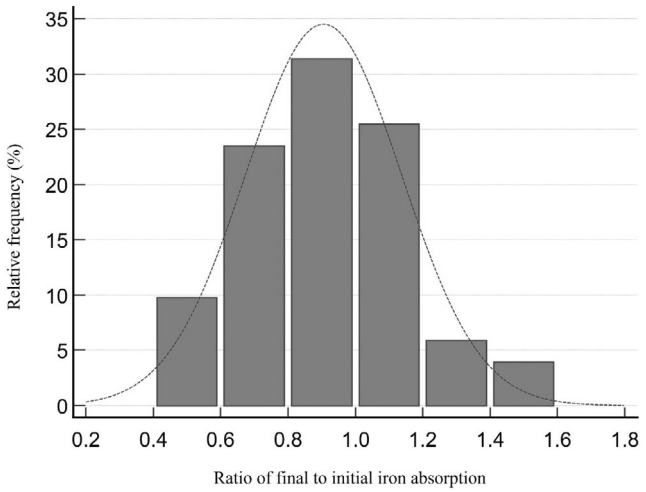

FIGURE 1 Distribution of change in iron absorption intensity after semaglutide introduction (expressed as the ratio of final to initial absorption). The x-axis shows the iron absorption (IA) ratio at 10 weeks compared to baseline, calculated as IA at 10 weeks divided by IA at baseline. A ratio below 1 indicates reduced IA after semaglutide treatment, while a ratio above 1 indicates improved absorption. The shift of the curve to the left reflects an overall reduction in IA for most patients.

significant difference in iron absorption within the same subject, comparing measurements taken before and 10 weeks after the weekly subcutaneous administration of semaglutide, was defined as a change of 30%.[11]

No other medications, apart from semaglutide, were changed during the study period. Statistical analyses were conducted using non-parametric tests to assess differences before and after semaglutide treatment. Spearman's correlation and linear regression analyses were performed to identify potential predictors of iron absorption dynamics.

3 | RESULTS

A total of 51 T2DM subjects, aged between 45 and 65, were included in the study. Before the introduction of semaglutide, OIAT demonstrated a statistically significant median increase, the difference compared to baseline values, in evaluated parameters: 19% in serum iron concentration (median 17 vs 14 μmol/L, $p < 0.001$), 17% in TSAT (median 26.6 vs 21.7%, $p < 0.001$) and 3% in ferritin (median 123 vs 120 μg/L, $p < 0.001$). After 10 weeks of semaglutide therapy, these increases were significantly attenuated: 8% in iron (median 14 vs 13 μmol/L, $p = 0.013$), 7% in TSAT (median 20.6 vs 20%, $p = 0.013$) and 2% in ferritin (median 120 vs 117 μg/L, $p < 0.001$). Table 1 summarizes the data collected before and 10 weeks after initiating parenterally administered semaglutide. The median relative reduction in iron absorption following semaglutide initiation was 13% compared to their absorption levels before treatment. A total of 9 out of 51 (17.6%) participants experienced at least a 30% reduction in iron absorption with semaglutide therapy compared to the period before drug administration. The distribution of the percentage change in iron absorption after the introduction of semaglutide is shown in Figure 1. Univariate analyses identified lower body weight ($p = 0.031$), lower ferritin ($p = 0.048$) and prior exposure to sodium-glucose co-transporter-2 (SGLT-2) inhibitors ($p = 0.036$) as predictors of improved iron absorption. Multivariate analysis confirmed that lower body weight ($\beta = -0.004$, $r_{semipartial} = 0.27$, $p = 0.043$) and lower ferritin ($\beta = -0.002$, $r_{semipartial} = 0.36$, $p = 0.008$) independently predicted better iron absorption. However, no significant predictors of semaglutide-induced changes in iron absorption were identified.

4 | CONCLUSIONS

This study is the first to analyse the influence of subcutaneous semaglutide on intestinal iron absorption, and it provides novel insights into the potential effects of semaglutide on iron metabolism. Our results indicate that the increase in iron levels after OIAT is notably diminished following the introduction of semaglutide into the treatment. These results have important clinical implications, as diminished iron absorption could contribute to iron deficiency and anaemia in susceptible individuals.[3] Patients undergoing semaglutide treatment may require closer monitoring of iron status, particularly those with preexisting iron deficiency or increased iron requirements. In cases where iron supplementation is necessary, higher oral doses or parenteral formulations may be necessary due to compromised gastrointestinal

absorption. Further research is warranted to confirm these findings in larger cohorts and explore semaglutide's long-term effects on iron homeostasis.

This study raises important questions regarding the broader metabolic effects of GLP-1 RAs beyond glucose control. The potential interactions between semaglutide and other micronutrients, particularly those dependent on gastrointestinal absorption, should be further explored. Predictors of better iron absorption were lower body weight, lower body mass index, lower ferritin and exposure to SGLT-2 inhibitors. Thus, a higher amount of ingested iron relative to body weight, as well as lower iron reserves, resulted in better iron absorption. The association between SGLT-2 inhibitors and better iron absorption at baseline is of special interest, since this drug class is known to promote erythropoiesis and, therefore, may influence better iron utilization and absorption.[12] Due to the study design, all patients served as their own controls, diminishing the contribution of parameters influencing differences in iron absorption at specific time points, as they did not significantly affect the dynamics of absorption change over time. Finally, further studies should include a control group, either a placebo or an active comparator, to achieve significantly higher-quality results through a two-armed trial.

Our study had several limitations. First, the dietary intake and potential changes in nutritional habits after the initiation of semaglutide were not systematically assessed. Second, relying solely on the OIAT to quantify absorption may overlook the dynamics of iron absorption. Using radiolabeled iron and more frequent measurements could improve the quantification of this process. Additionally, the relatively short follow-up period limited our ability to assess long-term changes in iron metabolism. Furthermore, the modest sample size indicates that larger studies are needed to validate our findings and determine their generalizability. Finally, future studies should include a control group, either placebo or active comparator, to achieve significantly higher-quality results through a two-armed trial.

In conclusion, semaglutide therapy offers significant benefits in glycemic control and weight reduction; however, its potential impact on iron absorption warrants further investigation. Clinicians should remain vigilant in monitoring iron parameters in patients receiving semaglutide, particularly those at risk of deficiency. Optimizing iron supplementation strategies in this context could improve overall patient outcomes and prevent unintended complications associated with impaired iron metabolism.

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The authors have no potential conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

The trial data is available on request from the authors.

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