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Effects of semaglutide in patients with chronic ankle instability: evidence from a prospective cohort

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Abstract

Background Whether patients with chronic ankle instability (CAI) can benefit from weight loss yielded by using glucagon-like peptide-1 receptor agonists (GLP1-RAs) has remained unclear.

Methods In this observational study, we recruited more than 2000 adults with CAI according to the selection criteria proposed by International Ankle Consortium with at least two-year follow up from three medical centers. The primary endpoint was the change from baseline of the Foot and Ankle Ability Measure (FAAM) sports subscale at the last follow up. Secondary endpoints included the change from baseline of Foot and Ankle Outcome Score (FAOS)/ Cumberland Ankle Instability Tool (CAIT)/ FAAM activities of daily living (ADL) subscale, number of ankle sprains during study period, incident ankle surgery in treatment of CAI.

Results In this study, 71 out of 2018 patients who received semaglutide in purpose of treating type 2 diabetes (T2DM) and/or weight loss during the study period. After controlling baseline characteristics, the adjusted mean difference in change from baseline was 16.3 for FAAM sports subscale and 9.3 for FAAM ADL subscale. Likewise, the adjusted analysis of five subscales of FAOS showed similar results, all consistently favoring semaglutide group. For CAIT, patients in the semaglutide group had achieved statistically significant improvement compared with control group. The association of semaglutide exposure with improvement in FAAM sports and ADL subscales was mediated by the weight loss measured by BMI (mediation proportion: FAAM sports subscale, 31.2% [22.2–41.2%]; FHSQ ADL subscale, 34.1% [24.4–44.8%]). We also observed statistically significant decreases in number of recurrent ankle

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sprains during study period. For incident ankle surgery, 1 out of 71 patients (1.4%) and 151 out of 1947 patients (7.8%) received ankle surgeries in semaglutide and control groups, respectively ($P=0.047$).

Conclusions Semaglutide may show potential benefits as a supplementary intervention in treatment of CAI by improving patient-reported outcomes and preventing recurrent ankle sprains. Further randomized trial is warranted by the current study to further confirm our findings.

Trial registration researchregistry10716.

Keywords Chronic ankle instability, Ankle sprain, Semaglutide, GLP-1 receptor agonist, Weight loss

Introduction

Lateral ankle sprain (LAS) is a common type of musculoskeletal injuries observed in the general population [1, 2]. Among these individuals, LAS could eventually progress to chronic ankle instability (CAI) in from 10 to 40% patients according to previous reports [1]. The typical symptoms and sequelae of CAI included pain, persistent swelling, ankle "giving-way", risks of recurrent injury and impaired joint function [1, 3]. As a result, CAI has a substantially negative impact on general health-related quality of life, working performance and recreational activities [4, 5]. Patients with severe CAI generally need surgical interventions to avoid repeated ankle sprains, osteochondral injuries and ankle osteoarthritis [6, 7].

Obesity and overweight are well-established risk factors for CAI development and reducing body weight was an effective measure against CAI progression [8]. Although body weight is clearly a modifiable factor, traditional options for weight management including dietary restriction and physical exercise might be challenging and less cost-effective for many CAI patients [9–11]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) including semaglutide and tirzepatide are effective and safe options for type 2 diabetes (T2DM) and weight control by stimulating delaying gastric emptying and decreasing appetite [12–15]. Thus, we believe patients with CAI might benefit from GLP-1RA exposure and, to the best of our knowledge, no previous study has focused the therapeutic potentials of GLP-1RAs on CAI.

Methods

Study design

This study was approved by the ethics committee at our institutions and written informed consent was obtained from all participants before enrollment. This study complied with the Declaration of Helsinki for research. We performed analysis and reported the findings according to the STROCSS criteria [16].

Participants

This study was approved by the ethics committee at our institution and written informed consent was obtained from all participants before enrollment. This study complied with the Declaration of Helsinki for research. From Jan 1, 2020 to Jan 1, 2022, we enrolled a total of 2323 patients with CAI from Shanghai Sixth People's Hospital, Shanghai Sixth People's Hospital East Campus and Ningbo No. 6 Hospital. Participants were excluded from the final analysis if they had GLP-1RA exposure before enrollment ($n=13$), receiving other GLP-1RAs during study period ($n=15$), follow up less than two years ($n=177$), bilateral CAI ($n=64$), autoimmune diseases ($n=2$), infections or tumors of the lower extremity ($n=6$), neurological or vascular abnormality affecting the lower extremity ($n=5$) and surgery history of lower extremity at baseline ($n=23$) (Fig. 1). The diagnosis of CAI was made by specialists in orthopedic surgery and/or sports medicine according to the selection criteria proposed by International Ankle Consortium (IAC) [17]. Briefly, for the optional part of IAC selection criteria, we adopted Cumberland Ankle Instability Tool (CAIT) < 24 and Foot and Ankle Ability Measure (FAAM) activities of daily living (ADL) subscale < 90% and sports subscale < 80%. In this study, patients were grouped by receiving semaglutide or not in purpose of treating T2DM and weight management. Notably, semaglutide was not commercially available until early 2022 in China [18, 19]. Progressive balance training (BAL) and hip strengthening (HIP) both enhance balance and function in patients with CAI [20]. We documented whether patients received the indicated treatments during the study period.

Baseline data and patient-reported outcomes

Demographic and clinical features at baseline including sex, age and comorbidities were self-reported by the participants. Height and weight were measured and recorded by researchers and then body mass index (BMI) was calculated. To determine the possible mechanical stability, physical examination including the anterior drawer test and inversion talar tilt test were performed manually. The examiners graded the amount of displacement with Grade I as stable joint, II as partially unstable, and III as completely unstable [21–23]. Throughout the study period, the participants were managed, assessed, and followed up by experienced and trained foot and ankle surgeons.

The FAAM is a 29-item questionnaire to assess physical function for individuals with foot and ankle related

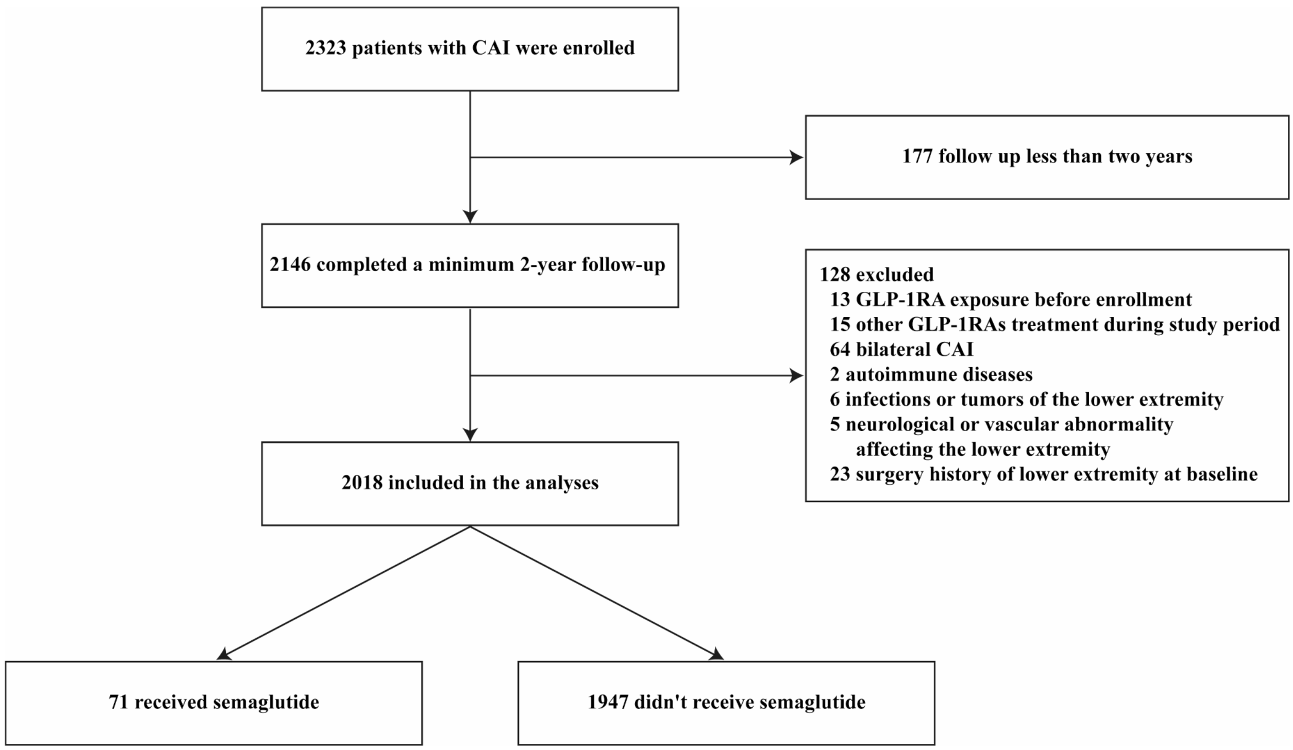

Fig. 1 Flow chart of the study

impairments with two subscales (ADL, [21 items] and sports [8-item]) [24]. The Foot and Ankle Outcome Score (FAOS) is a 42-item questionnaire on five subscales: pain (9 items), symptom (7 items), ADL (17 items), sports (5 items), and foot and ankle related quality of life (QoL, 4 items) [25]. The subscale scores of FAAM and FAOS were calculated by summing up all items in each subscale and then normalizing into a scale from 0 to 100, higher score indicating the better outcomes. The CAIT [26, 27] is a 9-item 30-point scale, for measuring severity of functional ankle instability, higher score indicating higher stability.

Follow-up

Participants were routinely followed up once per year by phone call and/or WeChat, a popular free messaging app in China. All patient-reported outcomes were collected at each follow up. The recurrent ankle sprain and ankle surgery was reported by patients. The definition of recurrent ankle sprain was incident ankle sprain to the same ankle during the study period. An acute traumatic injury to the lateral ligament complex of the ankle joint as a result of excessive inversion of the rear foot or a combined plantar flexion and adduction of the foot was considered as 'ankle sprain' according to the recommendations from a previous study [28]. The incident ankle surgery was defined as all types of surgeries in purpose of treating CAI. The last follow-up outcomes before surgery would be carried forward if surgery was performed.

Statistical analysis

Continuous and categorical variables are presented as means ± SD and counts (percentages), unless otherwise indicated. All statistical assessments were performed in a two-sided fashion. When *P* value was less than 0.05, the result would be considered as statistically significant. Statistical analysis was conducted using IBM SPSS V.26.0, and the 'mediation' package in R V.4.1.2 was applied for mediation analysis in this study. Use inverse probability weighting (IPW) to balance baseline characteristics, including BMI, T2DM status and so on. Statistical models were weighted to minimize bias of sample size discrepancy due to the low prevalence of GLP-1RA in China. Univariable analyses were first performed via the t-test (or Mann-Whitney U test) and Pearson's $\chi 2$ test or Fisher's exact t test. We also established an exposure-mediator-outcome model to assess weight loss as a mediator by dividing the total effect into the direct and indirect effects. We performed a model-based causal mediation analysis to calculate the proportion of indirect effect and its 95% confidence interval (CI) simulated by the quasi-Bayesian Monte Carlo method based on normal approximation [29]. The set of pre-exposure covariates (age, sex, BMI and baseline CAIT scores) satisfied the assumption of confounding adjustment for the exposure–mediator–outcome relationships (Fig. 2).

Results

Body weight and change from baseline in the semaglutide and control groups

In the final analysis, we included 71 participants who received semaglutide in purpose of treating T2DM ($n=31$) and/or weight loss ($n=66$). The baseline characteristics of patients grouped by semaglutide exposure were demonstrated in Table 1. The average follow-up period of the semaglutide group was (2.9 ± 0.7) months, while the control group (3.0 ± 0.7) months. The semaglutide and control groups had similar mean BMI at baseline (25.6 ± 3.7 figuerversus 25.0 ± 4.0, $P=0.215$). At the last follow up, patients in the semaglutide group had achieved substantial weight loss when compared with the control group (adjusted mean difference −3.4, 95% confidence interval [CI] [-2.9 to -3.9], $P<0.001$), favoring semaglutide (Table 2).

Comparison of pros between the semaglutide and control groups

Shown in Table 2, after controlling baseline characteristics including age, sex, BMI, T2DM and corresponding baseline score for each scale, the adjusted mean difference in change from baseline was 16.3 (95%CI, 13.2 to 19.3; $P<0.001$) for FAAM sports subscale and 9.3 (95%CI, 7.2 to 11.3; $P<0.001$) for FAAM ADL subscale. Likewise, the adjusted analysis of five subscales of FAOS showed similar results, with an adjusted mean difference of 2.3 (95% CI, 0.9 to 3.6, $P=0.001$) for pain subscale; 13.2 (95% CI, 9.5 to 16.8, $P<0.001$) for symptom subscale; 5.2 (95% CI, 2.1 to 8.3, $P=0.001$) for ADL subscale; 11.2 (95% CI, 8.1 to 14.2, $P<0.001$) for QoL subscale, all consistently favoring semaglutide group. For CAIT, patients in the semaglutide group had achieved statistically significant improvement compared with control group (adjusted mean difference [95% CI], 6.9 [6.4 to 7.4], $P<0.001$).

For subgroups by sex, the male participants had adjusted mean difference for FAAM sports change at 16.2 (95%CI, 11.6 to 20.8; $P<0.001$) and female participants had 16.2 (95%CI, 12.1 to 20.4; $P<0.001$).

Mediation analysis of indirect effect of semaglutide on pros via weight loss

Shown in Table 3; Fig. 2, the controlled direct effect on FAAM sports subscale and indirect effect mediated by weight loss were 12.2 (95% CI, 9.1 to 15.4) and 4.0 (95% CI, 2.9 to 5.3), respectively. Likewise, for FAAM ADL subscale, the direct and indirect effects were 6.4 (95% CI, 4.3 to 8.4) and 2.9 (95% CI, 2.1 to 3.8). The association of semaglutide exposure with improvement in FAAM sports and ADL subscales was mediated by the weight loss measured by BMI (mediation proportion: FAAM sports subscale, 31.2% [22.2–41.2%]; FHSQ ADL subscale, 34.1% [24.4–44.8%]). This model was adjusted for age, sex, baseline BMI, T2DM and baseline corresponding scores.

Comparison of number of recurrent ankle sprains and incident ankle surgery between the semaglutide and control groups

Shown in Table 2, we observed statistically significant decreases in number of recurrent ankle sprains during study period (adjusted mean difference [95% CI], -0.5 [-0.7, -0.3], $P<0.001$) and number of recurrent ankle sprains per year (-0.2 [-0.2, -0.1], $P<0.001$) in the semaglutide group. For incident ankle surgery, only 1 out of 71 patients (1.4%) received surgical interventions in treatment of CAI while, in the control group, 151 out of 1947 patients (7.8%) received ankle surgeries ($P=0.047$). Table 4 presents the results of patients who received physical therapy (BAL and HIP) during the study period.

Discussion

The semaglutide was approved in the Chinese Mainland in 2021 and the exposures of other GLP-1RAs were found in less than 0.5% of the general population before 2022

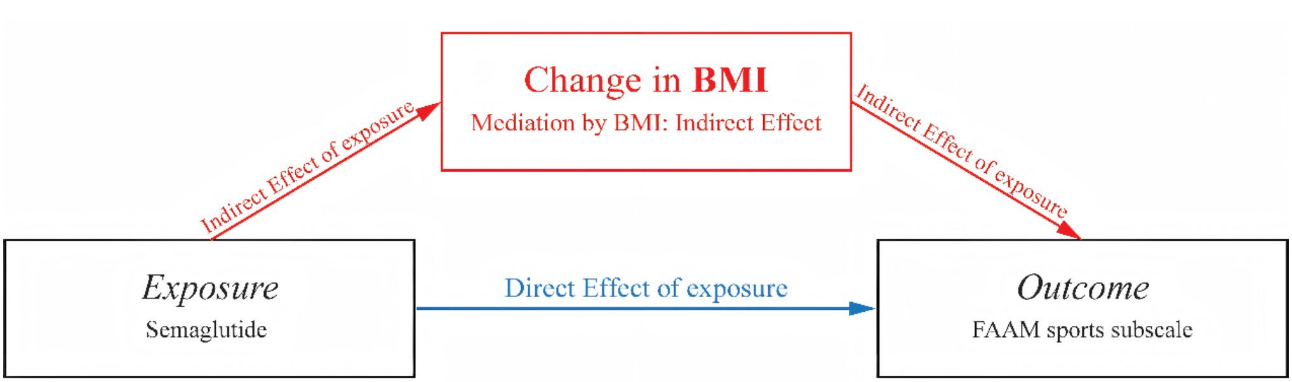

Fig. 2 Directed acyclic graph for mediation relationships

Table 1 Baseline characteristics of patients grouped by semaglutide exposure

	Semaglutide ($n=71$)	Control ($n=1947$)	P value
Age, years	38.0 ± 7.8	36.7 ± 7.6	0.154
Sex, No. (%)			
Male	33 (46.5)	776 (39.9)	0.263
Female	38 (53.5)	1171 (60.1)	
BMI, kg/m^2	25.6 ± 3.7	25.0 ± 4.0	0.215
Duration since the first ankle sprain, months	47.7 ± 20.8	47.1 ± 19.2	0.810
Duration since the last ankle sprain, months	19.5 ± 15.5	20.1 ± 14.9	0.748
Hypertension, No. (%)			
Yes	15 (21.1)	347 (17.8)	0.476
No	56 (78.9)	1600 (82.2)	
Smoking			
Yes	6 (8.5)	212 (10.9)	0.516
No	65 (91.5)	1735 (89.1)	
Grades of anterior drawer test, No. (%)			
I (stable)	38 (53.6)	1142 (58.7)	0.587
II (partially unstable)	28 (39.4)	653 (33.5)	
III (completely unstable)	5 (7.0)	152 (7.8)	
Inversion talar tilt test, No. (%)			
I (stable)	51 (71.8)	1497 (76.9)	0.576
II (partially unstable)	18 (25.4)	414 (21.3)	
III (completely unstable)	2 (2.8)	36 (1.8)	
T2DM, No. (%)			
Yes	31 (43.7)	157 (8.1)	< 0.001
No	40 (56.3)	1790 (91.9)	
FAAM sports subscale	63.1 ± 14.2	63.0 ± 14.4	0.952
FAAM ADL subscale	72.9 ± 11.8	71.4 ± 11.4	0.282
FAOS pain subscale	83.9 ± 8.9	82.3 ± 9.3	0.160
FAOS symptom subscale	69.3 ± 14.3	70.4 ± 15.5	0.577
FAOS ADL subscale	74.7 ± 14.3	72.6 ± 12.5	0.228
FAOS sports subscale	62.8 ± 14.3	63.7 ± 13.6	0.610
FAOS QoL subscale	54.2 ± 13.3	56.2 ± 15.6	0.297
CAIT	15.5 ± 4.3	15.8 ± 4.4	0.532

Data are shown as means (± SD) unless otherwise indicated. BMI, body mass index; FAAM, Foot and Ankle Ability Measure; FAOS, Foot and Ankle Outcome Score; ADL, activities of daily living; QoL, quality of life; CAIT, Cumberland Ankle Instability Tool

[18,19]. These facts gave us a unique research opportunity to explore the potential effects of semaglutide on CAI. As a result, we here only needed to exclude 13 out of 2323 participants from the final analysis because of GLP-1RA exposure before enrollment, without introducing substantial selection bias. Here we for first time reported that semaglutide might have potential effects of on CAI. After semaglutide exposure, patients achieved substantial improvement in terms of several PROs including FAAM, FAOS and CAIT when compared with control patients without semaglutide exposure. In addition to the improvement on PROs, number of ankle sprains during study period decreased significantly after using semaglutide. Finally, semaglutide resulted in a lower incidence of ankle surgery in treatment of CAI.

A previous meta-analysis confirmed that higher BMI was a great risk factor for CAI development after sustaining a LAS [30]. Controlling and reducing body weight was considered as a useful strategy for managing CAI and preventing recurrence injuries in CAI population [31]. The largest-to-date epidemiological study involving 829,791 participants demonstrated an increased BMI was more closely associated with CAI in females (overweight, OR 1.989, $P < 0.001$; obesity, OR 2.754, $P < 0.001$) when compared with males (overweight, odds ratio [OR] 1.249, $P < 0.001$; obesity, OR 1.418, $P < 0.001$). In this study, we did not observe the efficacy of semaglutide varied by sex according to our subgroup analysis.

Although dietary and physical interventions are the cornerstones of weight management, weight loss remains challenging for many of CAI patients due to the limited sports capability [32, 33]. Semaglutide, as one of the GLP-1RAs, is an effective and FDA-approved treatment

Table 2 Comparison of pros and clinically meaningful events between semaglutide and control groups

	Semaglutide (*n* = 71)	Control (*n* = 1947)	Adjusted mean difference (95% CI) *	Adjusted *P* value*
Follow-up, years	2.9 ± 0.7	3.0 ± 0.7		
BMI, kg/m^2				
At last follow-up	23.1 ± 4.8	25.9 ± 4.5		
Change from baseline	-2.6 ± 3.1	0.9 ± 2.0	-3.4 (-2.9, -3.9)	< 0.001
FAAM sports subscale				
At last follow-up	84.7 ± 15.4	68.0 ± 19.5		
Change from baseline	21.6 ± 9.9	5.0 ± 12.6	16.3 (13.2, 19.3)	< 0.001
FAAM ADLsubscale				
At last follow-up	86.5 ± 12.3	75.5 ± 14.0		
Change from baseline	13.6 ± 7.0	4.2 ± 8.3	9.3 (7.2, 11.3)	< 0.001
FAOS pain subscale				
At last follow-up	89.9 ± 6.0	87.4 ± 5.5		
Change from baseline	6.0 ± 11.1	5.5 ± 10.8	2.3 (0.9, 3.6)	0.001
FAOS symptom subscale				
At last follow-up	81.6 ± 16.5	69.3 ± 20.9		
Change from baseline	12.3 ± 13.7	-1.1 ± 15.2	13.2 (9.5, 16.8)	< 0.001
FAOS ADL subscale				
At last follow-up	88.0 ± 10.9	83.1 ± 12.8		
Change from baseline	13.3 ± 15.8	10.5 ± 17.8	5.2 (2.1, 8.3)	0.001
FAOS sports subscale				
At last follow-up	80.6 ± 16.1	69.8 ± 15.1		
Change from baseline	17.8 ± 19.8	6.1 ± 20.2	10.2 (6.5, 13.9)	< 0.001
FAOS QoL subscale				
At last follow-up	73.8 ± 16.6	64.2 ± 17.4		
Change from baseline	19.5 ± 13.1	8.0 ± 12.9	11.2 (8.1, 14.2)	< 0.001
CAIT				
At last follow-up	23.9 ± 4.4	17.3 ± 4.8		
Change from baseline	8.4 ± 2.7	1.5 ± 2.0	6.9 (6.4, 7.4)	< 0.001
Number of ankle sprains during study period	0.3 ± 0.4	0.8 ± 0.8	-0.5 (-0.7, -0.3)	< 0.001
Number of ankle sprains during per year	0.1 ± 0.2	0.3 ± 0.3	-0.2 (-0.2, -0.1)	< 0.001
Incident ankle surgery	1 (1.4)	151 (7.8)		0.047

Data are shown as means (± SD) unless otherwise indicated. BMI, body mass index; FAAM, Foot and Ankle Ability Measure; FAOS, Foot and Ankle Outcome Score; ADL, activities of daily living; QoL, quality of life; CAIT, Cumberland Ankle Instability Tool. * Mean difference and *P* value adjusted for age, sex, baseline BMI, T2DM and corresponding baseline scores, if existed

Table 3 Direct effect of semaglutide and indirect effect mediated by weight loss

Exposure: Semaglutide	**Mediator: Change in BMI Endpoint: Change in FAAM sports subscale***
Controlled direct effect	12.2 (9.1, 15.4)
Indirect effect	4.0 (2.9, 5.3)
Total effect	16.3 (13.2, 19.3)
Proportion mediated	31.2% (22.2%, 41.2%)
Exposure: Semaglutide	**Mediator: Change in BMI Endpoint: Change in FAAM ADL subscale***
Controlled direct effect	6.4 (4.3, 8.4)
Indirect effect	2.9 (2.1, 3.8)
Total effect	9.2 (7.2, 11.3)
Proportion mediated	34.1% (24.4%, 44.8%)

FAAM, Foot and Ankle Ability Measure; ADL, activities of daily living. * The model was adjusted for age, sex, baseline BMI, T2DM and baseline corresponding scores

Table 4 Comparison of physical therapy between semaglutide and control groups

	Semaglutide (*n* = 71)	Control (*n* = 1947)	Adjusted *P* value*
Balance training	25 (35.2)	748 (38.4)	0.59
Hip strengthening	21 (29.6)	665 (34.2)	0.42

* Mean difference and *P* value adjusted for age, sex, baseline BMI, T2DM and corresponding baseline scores, if existed

option for weight control mainly by suppressing appetite [13–15]. The long-term safety for 2.4 mg semaglutide has been well-established by SELECT trial, a large-scale trial with more than 15,000 participants and a mean follow-up of 39.8 months [34] and serial STEP trials [14, 35]. The major adverse events were gastrointestinal adverse events, which were mostly mild to moderate [14, 34, 35]. Together, with previous and current evidence, we believe for those patients with CAI, when weight-losing and other indications for GLP-1RAs exists, physicians should inform patients of such a therapeutic option for better clinical decision, especially before surgical interventions.

The current study has several limitations. First, there is residual confounding bias due to the design of observational study, such as socioeconomic factors and disparities in drug accessibility. Unmeasured confounders such as exercise habits cannot be fully excluded. Although we have adjusted our analysis for T2DM and baseline BMI, indication bias remained inevitable due to its observational nature. GLP-1RAs were a class of drug just emerging in the recent years. Currently, 2.4 mg semaglutide was not covered by the National Medical Insurance System in China [36]. It is reasonable to speculate that those patients with higher socioeconomical status were more likely to use such drugs. Additionally, sample size imbalance may lead to potential impact of on statistical power, particularly in the T2DM subgroup (only 31 cases). Only 31 patients in this study had T2DM with semaglutide exposure, making the sample size too small to conduct a subgroup analysis to verify the efficacy of semaglutide. Future randomized trials are still needed to further validate our findings in this study. This study would not establish any confirmatory conclusions on the efficacy of GLP-1RA therapies on CAI. Second, our conclusions were proposed largely based on the PROs including FAAM, FAOS and CAIT. However, the minimal clinically important differences for these tools were ill-defined, especially for CAI. Therefore, although we observed larges estimates in our analyses, it remains uncertain for their clinical importance. Third, postoperative data were not collected in this study, and we did not assess the impact of semaglutide in patients who underwent ankle surgery. Finally, there is also lack of standardization in semaglutide dosage and treatment duration. Because this is an observational study, the dose and duration of semaglutide varied by patient preference, especially in those patients using semaglutide for weight loss.

Conclusion

In conclusion, patients with CAI might benefit from semaglutide usage by improving patient-reported outcomes and preventing recurrent sprains. Notably, this is also the first investigation which reported a pharmaceutical mean in treating CAI. Further randomized trial is warranted by our study to further evaluate the therapeutic effects of GLP-1RAs on CAI.

Abbreviations

CAI	Chronic ankle instability
GLP1-RAs	Glucagon-like peptide-1 receptor agonists
FAAM	Foot and ankle ability measure
FAOS	Foot and ankle outcome score
CAIT	Cumberland ankle instability tool
ADL	Activities of daily living
T2DM	Type 2 diabetes
LAS	Lateral ankle sprain
IAC	International Ankle Consortium
BAL	Balance training
HIP	Hip strengthening
BMI	Body mass index
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-025-05664-9 .

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

JZ, CW and JW contributed equally to this work. JZ, CW, JW, HZ, and ZS designed the study. All authors were involved in analysing and interpreting the data. JZ, CW, and JW drafted the manuscript. HZ, XM and ZS critically revised the manuscript for important intellectual content. WG and HW did the statistical analysis. XM and ZS obtained funding and provided administrative support. XM and ZS supervised the study. The corresponding author attested that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JZ, CW, HZ, and ZS are the guarantors. JZ, CW, HZ, and ZS have directly accessed and verified the underlying data reported in the manuscript. All authors critically reviewed this manuscript and provided final approval for publication. The corresponding author had full access to the data and the final responsibility to submit for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Shanghai Sixth People's Hospital (approval no. 2019-084). Moreover, this study complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for research involving humans. Written consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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