

Supplementary Appendix: Insights into the mechanism of action of tirzepatide: a narrative review

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Table S1. Impact of tirzepatide on appetite- and food-related assessments from phase 1 clinical trials in adults with obesity or overweight, with and without type 2 diabetes

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Overall Appetite Score	vs placebo: ↓ [1-3] vs liraglutide: ↓ [2] vs semaglutide: ↔ [1]	vs placebo: ↓ [3]		vs placebo: ↔ [2] vs liraglutide: ↔ [2]	vs placebo: ↓ [2, 3] vs liraglutide: ↓ [2]
Satiety	vs placebo: ↑ [1, 2] or ↔ [3] vs liraglutide: ↑ [2] vs semaglutide: ↔ [1]	vs placebo: ↔ [3]		vs placebo: ↔ [2] vs liraglutide: ↔ [2]	vs placebo: ↑ [3] or ↔ [2] vs liraglutide: ↔ [2]
Fullness	vs placebo: ↔ [1, 3] or ↑ [2] vs liraglutide: ↑ [2] vs semaglutide: ↔ [1]	vs placebo: ↑ [3]		vs placebo: ↔ [2] vs liraglutide: ↔ [2]	vs placebo: ↑ [2] or ↔ [3] vs liraglutide: ↔ [2]
Hunger	vs placebo: ↓ [2, 3] or ↔ [1] vs liraglutide: ↓ [2] vs semaglutide: ↔ [1]	vs placebo: ↓ [3]		vs placebo: ↔ [2] vs liraglutide: ↔ [2]	vs placebo: ↓ [2, 3] vs liraglutide: ↓ [2]
Prospective food consumption	vs placebo: ↓ [1-3] vs liraglutide: ↓ [2] vs semaglutide: ↔ [1]	vs placebo: ↓ [3]		vs placebo: ↔ [2] vs liraglutide: ↔ [2]	vs placebo: ↓ [2, 3] vs liraglutide: ↓ [2]
Desire for sweet foods [2]	vs placebo: ↓ vs liraglutide: ↓			vs placebo: ↔ vs liraglutide: ↔	

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Desire for salty foods [2]	vs placebo: ↓ vs liraglutide: ↔			vs placebo: ↔ vs liraglutide: ↔	
Desire for savory foods [2]	vs placebo: ↔ vs liraglutide: ↓			vs placebo: ↔ vs liraglutide: ↔	
Desire for fatty foods [2]	vs placebo: ↓ vs liraglutide: ↓			vs placebo: ↔ vs liraglutide: ↔	
Extended Food Craving Inventory (FCI)^a [2]	vs placebo: ↓ vs liraglutide: ↓				
High fats	vs placebo: ↓ vs liraglutide: ↔		vs placebo: ↓ vs liraglutide ↔		
Sweets	vs placebo: ↓ vs liraglutide: ↓		vs placebo: ↓ vs liraglutide: ↓		
Carbohydrates/starches	vs placebo: ↓ vs liraglutide: ↔		vs placebo: ↓ vs liraglutide ↔		
Fast-food fats	vs placebo: ↓ vs liraglutide: ↔		vs placebo: ↓ vs liraglutide ↔		
Fruits and vegetables	vs placebo: ↔ vs liraglutide: ↔		vs placebo: ↓ vs liraglutide ↔		
Food Preference Questionnaire (FPQ) [4]					
High fat			vs placebo: ↓		

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Low fat			vs placebo: ↓		
High simple sugar			vs placebo: ↓		
High complex carbohydrates			vs placebo: ↓		
Low carbohydrates/high protein			vs placebo: ↓		
High fat/high simple sugar			vs placebo: ↓		
High fat/high complex carbohydrates			vs placebo: ↓		
High fat/low carbohydrates/high protein			vs placebo: ↓		
Low fat/high simple sugar			vs placebo: ↔		
Low fat/high complex carbohydrates			vs placebo: ↓		
Low fat/low carbohydrates/high protein			vs placebo: ↓		
Fat preference			vs placebo: ↔		

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Food Craving Questionnaire-State (FCQ-S) [2]	vs placebo: ↓ vs liraglutide: ↓				
Psychological state (hunger)	vs placebo: ↓ vs liraglutide: ↓				
Lack of control	vs placebo: ↓ vs liraglutide: ↓				
Anticipation of negative reinforcement	vs placebo: ↓ vs liraglutide: ↔				
Anticipation of positive reinforcement	vs placebo: ↓ vs liraglutide: ↓				
Desire	vs placebo: ↓ vs liraglutide: ↓				
Eating Inventory^b [2]					
Cognitive restraint	vs placebo: ↔ vs liraglutide: ↔				
Disinhibition	vs placebo: ↓ vs liraglutide: ↓				
Perceived hunger	vs placebo: ↓ vs liraglutide: ↓				

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Power of Food Scale (PFS) [2]	vs placebo: ↓ vs liraglutide: ↓				
Food available	vs placebo: ↓ vs liraglutide: ↓				
Food present	vs placebo: ↓ vs liraglutide: ↓				
Food tasted	vs placebo: ↓ vs liraglutide: ↓				
Barrat Impulsiveness Scale (BIS-11) [2]	vs placebo: ↓ vs liraglutide: ↔				
<i>First-order effects</i>					
Attention	vs placebo: ↔ vs liraglutide: ↔				
Cognitive complexity	vs placebo: ↔ vs liraglutide: ↔				
Cognitive instability	vs placebo: ↓ vs liraglutide: ↔				
Self-control	vs placebo: ↔ vs liraglutide: ↔				
Motor impulsiveness	vs placebo: ↓ vs liraglutide: ↔				

Assessment	Fasting	During sMMTT	Random fed	Postprandial	Retrospective
Perseverance	vs placebo: ↔ vs liraglutide: ↔				
Second-order effects					
Attentional	vs placebo: ↔				
impulsiveness	vs liraglutide: ↔				
Non-planning	vs placebo: ↔				
impulsiveness	vs liraglutide: ↔				
Motor impulsiveness	vs placebo: ↓ vs liraglutide: ↔				

See Table S2 for additional details about each of the instruments listed above.

BIS-11 Barrat Impulsiveness Scale version 11, *FCI* Food Craving Inventory, *FCQ-S* Food Craving Questionnaire-State, *FPQ* Food Preference Questionnaire, *PFS* Power of Food Scale, *sMMTT* standardized mixed meal tolerance test, *VAS* Visual Analog Scale.

^a In tirzepatide trials, the standard FCI questionnaire was adapted to include one additional factor evaluating the frequency of cravings for fruits and vegetables using 5 items, rated using the same scale used for the other factors (Never = 1, Rarely = 2, Sometimes = 3, Often = 4, Always = 5).

^b Eating Inventory is also known as the Three Factor Eating Questionnaire (TFEQ).

The effect of tirzepatide on food-related outcomes was assessed in three clinical trials:

- A secondary analysis of a 28-week mechanism-of-action, randomized, double-blind, parallel-arm study in adults with type 2 diabetes assessed the effects of tirzepatide 15 mg (N = 45), semaglutide 1 mg (N = 44), and placebo (N = 28) on fasting VAS ratings of hunger, satiety, fullness, and prospective food consumption after 28 weeks of treatment, and a composite of the four scores was used to calculate an overall appetite score [1].

- A 6-week phase 1, randomized, partially-blinded, parallel-design trial conducted in people without diabetes assessed the effects of tirzepatide (N = 37), liraglutide (N = 38), and placebo (N = 39) on VAS ratings of hunger, satiety, fullness, prospective food consumption, and desire for specific food before and after an ad libitum meal at baseline, after 3 weeks of treatment (comparing tirzepatide 5 mg and liraglutide 1.8 mg to placebo), and after 6 weeks of treatment (tirzepatide 10 mg and liraglutide 3 mg vs placebo) as well as retrospectively (average feelings over the previous week). The trial also assessed the effects of tirzepatide and liraglutide compared to placebo on cravings for specific food types (via the FCI); state cravings (via the FCQ-S); disinhibition, hunger, and cognitive restraint (via the Eating Inventory); susceptibility to food environment (via the PFS); and impulsiveness (via the BIS-11) in the fasted state at baseline, Week 3, and Week 6 [2].

- A phase 1, randomized, double-blind clinical trial in people with obesity without type 2 diabetes compared the effects of tirzepatide 15 mg (N = 27) versus placebo (N = 28) on VAS ratings of hunger, satiety, fullness, and prospective food consumption during an ad libitum test meal and sMMTT conducted at baseline and after 18 weeks of treatment. Retrospective VAS ratings of hunger, satiety, fullness, and prospective food consumption over the previous week were also assessed at baseline, weekly from Week 1 to 15, and at Week 18 of treatment [3]. Participants also completed the FPQ at baseline, Week 8, and Week 18. Tirzepatide significantly decreased food preference scores in 10 of 12 FPQ metrics at Week 8 and Week 18 compared with placebo. These data were previously disclosed as an oral presentation at the 2023 American Diabetes Association Scientific Sessions in San Diego, California [4].

Table S2. Validated tools used in phase 1 clinical trials of tirzepatide for the assessment of self-reported appetite- and food-related sensations

Tool name	Purpose	Method	Key features
Visual Analog Scale (VAS) [5-7]	Evaluates 4 appetite sensations: hunger, satiety, fullness, and prospective food consumption; desire for specific foods: sweet, salty, savory, and fatty	Participants self-report their rating to the following questions on either a 10-cm line or a 100-unit line represented on a piece of paper or a computer screen, ranging from 0-100. Values were anchored by verbal descriptors such as “not at all” to “extremely” for appetite sensations, and “yes, very much” to “not at all” for desire for specific foods. - Hunger: How hungry do you feel right now? - Satiety: How satisfied do you feel right now? - Fullness: How full do you feel right now? - Prospective food consumption: How much food do you think you could eat right now? Desire for specific foods: - Would you like to eat something sweet? - Would you like to eat something salty? - Would you like to eat something savory? - Would you like to eat something fatty?	Used to capture appetite-related metrics at the time of the scoring or in retrospect. Retrospective method of collecting VAS data has been found to be consistent with daily assessments of satiety.

Tool name	Purpose	Method	Key features
Overall Appetite Score [5]	Calculated from the 4 individual components of the appetite sensation VAS as continuous variables on the 0-100 scale	Calculated as the average of the 4 individual scores (satiety + fullness + [100-prospective food consumption] + [100-hunger]/4)	The higher the overall appetite score, the lower the appetite; conversely, the lower the score, the greater the appetite.
Food Craving Inventory (FCI)^a [8]	A 28-item self-report questionnaire to assess the frequency of cravings for general and specific foods. The FCI quantifies food cravings related to overeating and binge eating	This measure consists of rating of cravings for 28 items in 4 empirically derived factors: - high fats - sweets - carbohydrates/starches - fast-food fats Participants rate the frequency of craving and of actually eating the food(s) for each item in the past month using the following scale: Never = 1, Rarely = 2, Sometimes = 3, Often = 4, Always/Almost every time = 5.	
Food Preference Questionnaire (FPQ) [9]	Assesses preferences for 72 foods in a 2 (high fat, low fat) by 3 (high simple sugar, high complex carbohydrate, low carbohydrate/high protein) matrix	Participants rate each food hedonically on a 9-point Likert scale by rating how much they like each food, where 1 = dislike extremely, 5 = neither like nor dislike, and 9 = like extremely.	The FPQ has established reliability and validity.

Tool name	Purpose	Method	Key features
Food Craving Questionnaire-State (FCQ-S) [10, 11]	A 15-item measure that assesses the strength of state-dependent food cravings at the moment of administration	The questionnaire assesses 5 sub-scales of cravings: desire to eat, anticipation of positive reinforcement, anticipation of relief from negative feelings/states, lack of control, and hunger scores. Participants indicate the extent to which they agree with each statement right now, at this very moment, on a 5-point Likert scale, where 1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree. Scores are calculated by summing the score of each item on the sub-scale, or by summing up all 15 items for an overall score. Greater scores denote higher levels of craving.	The FCQ-S has demonstrated good validity and internal consistency in non-clinical populations at the time of provision. This assessment is sensitive to situational changes such as food deprivation and food intake.
Eating Inventory^b [12, 13]	A self-reported 51-item instrument assessing 3 eating-related constructs, cognitive and behavioral: - Dietary restraint: intent and ability to restrict food intake - Disinhibition: tendency to overeat - Perceived hunger:	In all, 36 items are true/false, 14 items are on a 1-4 Likert scale, and 1 item is on a 0-5 Likert scale. Scores for restraint, disinhibition, and hunger range from 0-21, 0-18, and 0-14, respectively, and a greater number indicates greater levels of each respective eating component.	

Tool name	Purpose	Method	Key features
	susceptibility to feelings of hunger		
Power of Food Scale (PFS) [14, 15]	Self-reported questionnaire used to assess the psychological impact of living in food-abundant environments; the focus is on appetite for, and not consumption of, palatable foods at 3 levels of food proximity (food available, food present, and food tasted).	A 15-item tool with 3 sub-scale domains: food available, food present, food about to be tasted. Response to questions based on a 5-point Likert scale (from 1 = don't agree at all to 5 = strongly agree). For each domain, the score is the mean score per item in each domain. The score for the aggregate domain is calculated as the mean of the 3 domain scores.	High internal consistency and test–retest reliability
Barrat Impulsiveness Scale 11 (BIS-11) [16, 17]	A 30-item self-reported questionnaire measuring impulsive or non-impulsive behaviors and preferences	Responses are scored on a Likert scale ranging from 1 = rarely or never to 4 = almost always or always; higher scores indicate greater impulsiveness. The scale consists of 6 first-order factors and 3 second-order factors. First-order factors: - attention (e.g.: focus on task at hand) - motor impulsiveness (e.g. acting on spur of the moment) - self-control (e.g. speaking out of turn) - cognitive complexity (e.g. being bored when not intellectually stimulated)	

Tool name	Purpose	Method	Key features
		- perseverance (e.g. consistent lifestyle) - cognitive instability (e.g. experiencing rapid or racing patterns of thought) Second-order factors: - attentional impulsiveness (difficulties with attention and rapid thoughts) - motor impulsiveness (trouble with motor impulsiveness and perseverance) - non-planning impulsiveness (trouble with self-control and cognitive complexity)	

^a In tirzepatide trials, the standard Food Craving Inventory questionnaire was adapted to include one additional factor evaluating the frequency of cravings for fruits and vegetables rated on the same Likert scale used for the other factors (Never = 1, Rarely = 2, Sometimes = 3, Often = 4, Always = 5).

^b Eating Inventory is also known as the Three Factor Eating Questionnaire (TFEQ).

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