

## Narrative Review

## Dietary impact on fasting and stimulated GLP-1 secretion in different metabolic conditions – a narrative review

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## A B S T R A C T

Glucagon-like peptide 1 (GLP-1), a gastrointestinal peptide and central mediator of glucose metabolism, is secreted by L cells in the intestine in response to food intake. Postprandial secretion of GLP-1 is triggered by nutrient-sensing via transporters and G-protein-coupled receptors (GPCRs). GLP-1 secretion may be lower in adults with obesity/overweight (OW) or type 2 diabetes mellitus (T2DM) than in those with normal glucose tolerance (NGT), but these findings are inconsistent. Because of the actions of GLP-1 on stimulating insulin secretion and promoting weight loss, GLP-1 and its analogs are used in pharmacologic preparations for the treatment of T2DM. However, physiologically stimulated GLP-1 secretion through the diet might be a preventive or synergistic method for improving glucose metabolism in individuals who are OW, or have impaired glucose tolerance (IGT) or T2DM. This narrative review focuses on fasting and postprandial GLP-1 secretion in individuals with different metabolic conditions and degrees of glucose intolerance. Further, the influence of relevant diet-related factors (e.g., specific diets, meal composition, and size, phytochemical content, and gut microbiome) that could affect fasting and postprandial GLP-1 secretion are discussed. Some studies showed diminished glucose- or meal-stimulated GLP-1 response in participants with T2DM, IGT, or OW compared with those with NGT, whereas other studies have reported an elevated or unchanged GLP-1 response in T2DM or IGT. Meal composition, especially the relationship between macronutrients and interventions targeting the microbiome can impact postprandial GLP-1 secretion, although it is not clear which macronutrients are strong stimulants of GLP-1. Moreover, glucose tolerance, antidiabetic treatment, grade of overweight/obesity, and sex were important factors influencing GLP-1 secretion. The results presented in this review highlight the potential of nutritional and physiologic stimulation of GLP-1 secretion. Further research on fasting and postprandial GLP-1 concentrations and the resulting metabolic consequences under different metabolic conditions is needed.

**Keywords:** glucagon-like peptide 1, type 2 diabetes mellitus, glucose tolerance, postprandial metabolism, meal challenge, human

## Introduction

Type 2 diabetes mellitus (T2DM), a major lifestyle-related disease, has been increasing in prevalence globally. T2DM is associated with several physical and psychological comorbidities and is a major health concern [1,2]. Obesity, particularly excessive fat accumulation in the abdomen, is an important risk factor for T2DM. Therefore, fighting obesity and T2DM has become a global goal, leading to increased

research in this field [3,4]. Nutrition plays a crucial role in addressing this challenge. This is because energy deficits can restore normal body weight and improve health. Moreover, a targeted selection of foods or nutrients can address specific therapeutic goals through various pathways. One potential mechanism through which diet can influence obesity and T2DM is through gastrointestinal peptide hormones, such as glucagon-like peptide 1 (GLP-1) [5]. GLP-1 has been shown to positively affect several factors related to obesity and T2DM, including

**Abbreviations:** AUC, area under the curve; CFU, colony-forming unit; CRHP, carbohydrate-reduced-high-protein; DPP-IV, dipeptidylpeptidase-4; FFAR, free-fatty acid receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GPCRs, G-protein-coupled receptors; HC, high-carbohydrate; iAUC, incremental area under the curve; IU, international units; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; MMTT, Mixed Meal Tolerance test; NGT, normal glucose tolerance; NW, normal weight; OGTT, oral glucose tolerance test; OW, overweight/obesity; RCT, randomized controlled trial; RIA, radioimmunoassay; T2DM, type 2 diabetes mellitus.

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pancreatic  $\beta$ -cell function, blood glucose homeostasis, satiety, and food intake [6–9]. These physiologic actions of GLP-1 indicate its high therapeutic potential. This, together with studies showing impaired GLP-1 secretion in T2DM, has led to the exploration of GLP-1 as a treatment option for T2DM over the last few decades. Although GLP-1 secretion seems to be reduced in obesity and T2DM, intravenous administration of GLP-1 analogs elicits metabolic responses similar to that of healthy individuals, suggestive of a preserved GLP-1 sensitivity in obesity and T2DM. Therefore, augmentation of endogenous GLP-1 secretion and administration of exogenous GLP-1 have become research targets. GLP-1 analogs [and dipeptidylpeptidase-4 (DPP-IV) inhibitors] have been successfully included in diabetes treatment for several years [7,9–13].

The secretion of GLP-1 is partly mediated by nutrient binding to G-protein-coupled receptors (GPCRs) or by absorption via membrane transporters, which are expressed by enteroendocrine L cells in the gastrointestinal tract. Thus, postprandial GLP-1 secretion also has therapeutic potential. Adjusting the diet in a way that increases the interaction with these molecules could enhance GLP-1 secretion and amplify its beneficial effects.

This review presents recent evidence on glucose- and food-dependent secretion of GLP-1 in individuals with different metabolic conditions, including obesity, impaired glucose tolerance (IGT), and T2DM, as well as its potential modulation through short- and long-term dietary approaches.

### Physiologic functions of GLP-1 inside the gut-brain-pancreas axis

GLP-1 is mainly synthesized and secreted by enteroendocrine L cells of the gastrointestinal tract, which are considered the key components of the gut-brain-pancreas axis [14]. Plasma concentrations of GLP-1 are low after an overnight fast and increase after food intake. Its postprandial secretion is partly mediated by direct nutrient sensing by GPCRs which may be activated by peptides, amino acids, mono-unsaturated fatty acids, polyunsaturated fatty acids, and SCFAs [15]. GLP-1 has also been shown to be triggered by monosaccharide substrates of the apical sodium-dependent glucose co-transporter (SGLT1) [16,17]. Results from in vitro and animal models have shown that nutrients and metabolites (e.g., SCFAs) derived from bacterial fermentation of dietary fiber can stimulate the secretion of GLP-1 via GPCR41 and GPCR43, also termed free-fatty acid receptors (FFAR) 2 and FFAR 3 [18–20]. In humans, nondigestible and fermentable dietary fibers have been shown to increase GLP-1 secretion [21–23]; however, the role of SCFAs remains unclear [24–27].

An important function of GLP-1 is as an incretin. The so-called incretin effect stimulates insulin secretion mediated by hormones released from the gastrointestinal tract—the incretin hormones, GLP-1, and the glucose-dependent insulinotropic polypeptide (GIP). This effect was observed when glucose was administered orally but not after intravenous infusion (which did not stimulate the secretion of incretin hormones) [28]. The magnitude of the “incretin effect” depends on the amount of glucose ingested [29]. Moreover, GLP-1 attenuates glucagon release, increases pancreatic  $\beta$ -cell mass, and regulates gastrointestinal motility by slowing down gastric emptying and enhancing satiety [30–33]. Therefore, an impaired GLP-1 secretion might contribute to the development of IGT and T2DM. However, the extent to which impaired GLP-1 secretion is involved in disease progression remains unclear.

Current studies suggest that GLP-1 plays a modulatory role in the regulation and maintenance of cognitive function, and a postprandial

increase in GLP-1 concentrations seems to contribute to neuroprotection. Hence, the physiologic stimulation of GLP-1 release by nutrients, diet, or changes in microbially produced metabolites may contribute to improved brain health [34]. These neuroprotective properties make GLP-1 an interesting target for nutritional intervention and further scientific investigation.

### GLP-1 secretion among individuals with different metabolic profiles

GLP-1 secretion has been widely studied in individuals with different metabolic profiles owing to its multiple beneficial properties for glucose homeostasis. Basal- and food-dependent GLP-1 secretion has been hypothesized to differ between healthy adults and adults with IGT or T2DM; however, the results are conflicting. Some studies have shown reduced basal or postprandial GLP-1 concentrations in patients with obesity or T2DM [35–38]. Simon et al. [37] found that the glucose-stimulated secretion of GLP-1 was lower in individuals with obesity than in their age- and sex-matched lean controls. Similar findings were reported in a large study involving 1400 individuals [39]. However, a recent meta-analysis of 18 studies showed that variations in fasting and postprandial GLP-1 secretion in people with and without T2DM were generally small and heterogeneous [40], although most studies suggested impaired secretion in individuals with obesity. Therefore, it is important to investigate GLP-1 secretion in individuals with different metabolic properties and degrees of glucose tolerance. To assess this association, both fasting and postprandial concentrations of glucose- and GLP-1 responses should be included.

### Methods

A literature search was performed according to standard procedures. We searched for human intervention studies published between 1996 and 2023 in PubMed that investigated glucose- or food-stimulated total GLP-1 secretion in 5 groups of participants; adults with normal weight, overweight/obesity (OW), normal glucose tolerance, impaired glucose tolerance, or T2DM. Studies were included only if they compared at least 2 of these groups. In addition, studies assessing the role of meal composition in GLP-1 secretion or the effects of short-, medium-, and long-term nutritional interventions, and probiotic, prebiotic, and synbiotic interventions on GLP-1 secretion in at least one of the listed groups of participants were included. The search terms are listed in [Supplemental Table 1](#). Filters applied were humans and clinical trials.

The following data were extracted according to data availability to assess the studies: fasting values of GLP-1, time, and concentration of the maximum values of postprandial GLP-1, and AUC and/or incremental area under the curve (iAUC) for participants grouped as healthy, OW, prediabetes, and diabetes. Data regarding AUC and/or iAUC were extracted from the studies when available. Studies that assessed fasting GLP-1 concentration and/or postprandial GLP-1 secretion after oral glucose tolerance test (OGTT), mixed meal tolerance test (MMTT), or challenge meals were included. In addition, studies assessing these outcomes before and after medium- or long-term interventions were included. The data used in this review are mainly original values that were provided by the corresponding authors (marked as #original data in the tables). If the original data values were not available and the authors could not be successfully contacted, GLP-1 values were estimated from graphs provided in articles, partly with the help of Web-PlotDigitizer (web-based Plot Digitizer, Copyright 2010–2020 Ankit Rohatgi, <https://apps.automeris.io/wpd/>).

## Glucose-stimulated GLP-1 response

Because GLP-1 secretion is consistently stimulated by glucose, the OGTT is an adequate tool for examining postprandial GLP-1 response. In this review, only studies that used the standard 75-g-glucose OGTT were included. Five different groups were considered for analysis; adults with normal weight (NW) or OW, NGT, IGT [including impaired fasting glucose (IFG)], and T2DM.

Table 1 [41–53] provides an overview of the results of the 13 studies included on fasting and peak values of glucose-stimulated GLP-1, the delta between both values, the time at which peak concentration is achieved, GLP-1 concentrations at selected time points, and the AUC or iAUC values (the GLP-1 concentrations measured at all time points are shown in Supplemental Table 2). In addition, details of the assays used for GLP-1 measurements are presented. Eight studies applied the same standardized assay based on radioimmunoassay (RIA) methodology [41]. Overall, across all participants and studies, the time taken to reach the maximum postprandial concentrations after the OGTT was between 20 and 90 min, and ranged from 10.5 and 69 pmol/L. In the NGT group, the time taken to reach maximum peak concentrations was between 20 [42,43] and 30 min [39,44–47], whereas in the IGT group, the time was between 30 [39,44,46,47] and 45 min [48], in T2DM group, the time was between 30 and 90 min (most studies observed a peak at 30 min) [39,44–47,49]. The results of these studies are shown as postprandial GLP-1 concentration curves in Figure 1. Theodorakis et al. [42] reported increased GLP-1 fasting values and AUC in T2DM compared with those in the NGT group [42]. These results were confirmed by Alssema et al. [44] and Chong et al. [50].

Dybjer et al. [51] also reported higher fasting GLP-1 concentrations in participants with unclassified T2DM than in nondiabetic controls; however, glucose-stimulated concentrations after 120 min were lower in participants with diabetes than in nondiabetic patients. Similarly, Muscelli et al. [45] showed reduced GLP-1 secretion in T2DM compared with that in IGT and NGT, whereas no significant differences were observed between the IGT and NGT groups. Given that GLP-1 and BMI are inversely related, a lack of significant differences in GLP-1 secretion between the IGT and NGT groups could be due to a similar mean BMI of the participants in these groups [45]. Wang et al. [46] also showed a comparable impaired GLP-1 response in individuals with NGT, IGT, or T2DM. In that study, the T2DM group showed distinctly reduced fasting/peak values and AUC ( $\leq 33\%$ ) than the NGT group. No significant differences were observed between the NGT and IGT groups. Færch et al. [39] found  $\leq 25\%$  reduced GLP-1 secretion in females with IFG or T2DM compared with females with NGT. In addition, in both males and females with IFG or T2DM, GLP-1 concentrations were reduced by 16%–21% after 120 min, independent of age and BMI. In this cohort, the GLP-1 response in individuals with obesity was reduced by 20% and in individuals with overweight by  $\leq 8\%$  compared with NW participants, independent of their glucose tolerance status. The authors concluded that impaired GLP-1 response can occur before developing obesity or T2DM. In the present study, higher GLP-1 concentrations were associated with better insulin sensitivity, older age, and a lower degree of OW. These findings aligned with the results of a study by Chia et al. [52], who found a reduced GLP-1 AUC in individuals who had OW compared with those who were of NW, although the fasted and peak values of GLP-1 did not differ between the NW and OW groups [52]. Similar findings were reported by Simon et al. [43]. Greenfield et al. [48] also showed a trend toward reduced fasted GLP-1 values and a lower AUC in the OW group compared with lean-matched controls. Moreover, this effect was

more distinct in groups with T2DM/IGT compared with NW and OW groups.

Vollmer et al. [49] detected no differences among the NGT, IGT, and T2DM groups. They described a positive association between GLP-1 response and increasing age and a negative association with higher BMI. Furthermore, higher concentrations of GLP-1 were found in females than in males. Two other studies found no differences in fasting/peak values and AUC between groups with NGT/OW and IGT/T2DM [47,53].

Of the 13 studies that were reviewed, a marked difference was observed in the time taken to reach peak GLP-1 concentrations after OGTT ingestion. Overall, the evidence shows that individuals with NGT attain a GLP-1 peak earlier than individuals with IGT or T2DM. Although OGTT is a highly standardized procedure, the results of the reviewed studies did not provide a conclusive answer as to whether fasting and postprandial GLP-1 values differed or were similar in individuals with disturbed glucose control than in healthy controls. Therefore, further research is needed to account for confounding factors such as BMI and sex.

## Food-stimulated GLP-1 response

Owing to the food-stimulated secretion of GLP-1, MMTTs, as a test meal containing all macronutrients, or a meal challenge are widely used in clinical research to monitor postprandial GLP-1 secretion [54]. In this part of the review, studies that used an MMTT with liquid or small-to-large solid challenge meals which were consumed within 10–15 min (as far as information was available) in participants with NGT, IGT, or T2DM were analyzed. Table 2 [55–58] presents the fasted and peak GLP-1 values, delta, time of reaching peak concentrations, AUC or iAUC values, and GLP-1 concentrations at selected time points after food ingestion (the GLP-1 concentrations at any available time points are shown in Supplemental Table 3), and information on the GLP-1 assays. Six of the 7 studies used the same RIA-based assay [41].

The maximum postprandial GLP-1 concentrations were reached between 15 and 150 min after MMTT or challenge meal ingestion and varied between 9.7 and 42 pmol/L.

Only one study used an MMTT (470 kcal) consisting of both a liquid plus a solid meal [237 mL Boost Drink (Nestlé) and a Power Bar (Nestlé)]. Fasting GLP-1 concentrations were 75 % higher in adults with T2DM than in those with NGT/IGT. The iAUC of total GLP-1 was higher in T2DM than in IGT (1200 pg\*min/mL compared with 2600 pg\*min/mL) but did not differ between NGT and IGT, or NGT and T2DM [55].

In contrast, several studies that used a solid meal for MMTT or challenge meal tests have reported impaired GLP-1 response in patients with (pre)diabetes. Vilsbøll et al. [56], investigated GLP-1 response after consumption of a small (260 kcal) compared with a large (520 kcal) western-styled breakfast meal consisting of a glass of milk and white and black bread with margarine, cheese, and jam. A reduced GLP-1 response was observed in T2DM patients when compared with matched NGT controls after both small and large meals [56]. These results were confirmed in the study by Alssema et al. [44] in which a reduced GLP-1 response was found in T2DM after consuming a western-styled breakfast consisting of 2 croissants with butter and cheese, full-fat milk, and a yogurt drink with soluble carbohydrates (maltose) (833 kcal) when compared with NGT/IGT. Moreover, there were no differences in GLP-1 response between the NGT and IGT groups. Rask et al. [57], also reported an impaired early GLP-1

**TABLE 1**

Glucose-stimulated GLP-1 response (OGTT)

Author, (y), <i>n</i>	GLP-1 assay	Participant characteristics	GLP-1 values (pmol/L) at time points (min)												TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC	Results
			0	10	15	20	30	40	45	60	90	120	180					
Theodorakis et al. 2006 [42] <i>n</i> = 53	RIA <sub>Linco</sub> <sup>1</sup>	NGT ( <i>n</i> = 36, BMI: 27 kg/m <sup>2</sup> )	6	15	21	22		21		16		11		20	16	120 min: AUC: 1874 (pmol/L*min) <sup>#</sup>	↑ fasting values and AUC in T2DM compared with NGT	
		T2DM ( <i>n</i> = 17, BMI: 30 kg/m <sup>2</sup> )	12	19	28	31		33		32		12		40	21	120 min: AUC: 2866 (pmol/L*min) <sup>#</sup>		
Muscelli et al. 2008 [45] <i>n</i> = 51	RIA <sup>2</sup>	NGT ( <i>n</i> = 24, BMI: 33.1 kg/m <sup>2</sup> ) <sup>#</sup>	11	18		27	28	25		25	22	23	23	30	17	180 min: AUC: 4100 (pmol/L*h) <sup>#</sup>	- ↓ GLP-1 response in T2DM compared with IGT and NGT	
		IGT ( <i>n</i> = 17, BMI: 35.9 kg/m <sup>2</sup> ) <sup>#</sup>	10	13		23	26	27		20	19	19	18	40	17	180 min: AUC: 3400 (pmol/L*h) <sup>#</sup>	- no significant differences between NGT and IGT	
		T2DM ( <i>n</i> = 10, BMI: 35.5 kg/m <sup>2</sup> ) <sup>#</sup>	7	10		13	12	13		11	12	12	9	20 40	6	180 min: AUC: 2000 (pmol/L*h) <sup>#</sup>	- inverse relationship between GLP-1 response and BMI	
Vollmer et al. 2008 [49] <i>n</i> = 48	RIA <sup>2</sup>	NGT ( <i>n</i> = 14, BMI: 27.5 kg/m <sup>2</sup> )	14				32			31	30	30	18	30	18	n.a.	- ↔	
		IGT ( <i>n</i> = 17, BMI: 29.5 kg/m <sup>2</sup> )	15				41			38	37	38	25	30	26		- positive relation between GLP-1 and age; negative association between GLP-1 concentrations and BMI	
		T2DM ( <i>n</i> = 17, BMI: 32.1 kg/m <sup>2</sup> )	16				35			33	39	28	23	90	23		- GLP-1 concentrations higher in females than in males	
Greenfield et al. 2009 [48] <i>n</i> = 24	RIA <sup>2</sup>	NW ( <i>n</i> = 8, BMI: 22 kg/m <sup>2</sup> )	14		30		32		27	27	27	24		30	18	120 min: AUC: 3192 iAUC: 1242 (pmol/L*120 min) <sup>#</sup>	↓ fasting values and AUC in T2DM/ IGT compared with NW/ OW	
		OW ( <i>n</i> = 8, BMI: 34.5 kg/m <sup>2</sup> )	13		22		24		22	23	21	18		30	11	120 min: AUC: 2550 iAUC:1082 (pmol/L* 120 min) <sup>#</sup>	↔ iAUC	
		T2DM/IGT ( <i>n</i> = 8, BMI: 38.5 kg/m <sup>2</sup> )	9		15		18		20	17	15	14		45	11	120 min: AUC: 1846 iAUC: 746 (pmol/L* 120 min) <sup>#</sup>		
Bagger et al. 2011 [53] <i>n</i> = 16	RIA <sup>2</sup>	OW ( <i>n</i> = 8, BMI: 29 kg/m <sup>2</sup> )	17	25		44	69		50	39		30	17	30	52	AUC: 7200 <sup>#</sup>	↔ fasting/ peak values, AUC	
		T2DM ( <i>n</i> = 8, BMI: 29 kg/m <sup>2</sup> )	20	30		51	47		48	38		31	17	20	31	AUC: 6900 <sup>#</sup> (4h* pmol/L)		
Alssema et al. 2013 [44] <i>n</i> = 203	RIA <sup>2</sup>	NGT ( <i>n</i> = 163, BMI: 26.7 kg/m <sup>2</sup> )	11		18		23			17	16	14		30	12	AUC: 18 iAUC: 7.3 (pmol/L per hour)	↑ fasting values and AUC per hour in T2DM compared with NGT	
		IGT ( <i>n</i> = 20, BMI: 28.5 kg/m <sup>2</sup> )	14		21		28			23	21	16		30	14	AUC: 21 iAUC: 6.7 (pmol/L per hour)		

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TABLE 1 (continued)

Author, (y), <i>n</i>	GLP-1 assay	Participant characteristics	GLP-1 values (pmol/L) at time points (min)												TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC	Results
			0	10	15	20	30	40	45	60	90	120	180					
Yabe et al. 2015 [47] <i>n</i> = 102	RIA <sup>2</sup>	T2DM ( <i>n</i> = 20, 33.1 kg/m <sup>2</sup> )		17		29		37		26	23	16		30	20	AUC: 23 iAUC: 6.5 (pmol/L per hour)	↔	
		NGT ( <i>n</i> = 54, BMI: 21.3 kg/m <sup>2</sup> )		9		17	19	19		17		16		20 30	10	120 min: AUC: 2004 (pmol/L*min)		
		IGT ( <i>n</i> = 20, BMI: 22.5 kg/m <sup>2</sup> )		8		12	16	17		15		14		30	9	120 min: AUC: 1701 (pmol/L*min)		
Færch et al. 2015 [39] <i>n</i> = 1462	RIA <sup>2</sup>	T2DM ( <i>n</i> = 28, BMI: 23.5 kg/m <sup>2</sup> )		10		17	18	18		18		14		20 30 40	8	120 min: AUC: 1923 (pmol/L*min)	- ↓GLP-1 response in IFG and T2DM (- up to25%) compared with NGT (females) - ↓120-min concentrations in IFG and T2DM (-16-21%) compared with NGT in persons with obesity (-20%) and OW (up to -8%) compared with NW participants	
		NGT ( <i>n</i> = 774, BMI: 26.0 kg/m <sup>2</sup> ) <sup>#</sup>	F	9			31				23		30	22	120 min: AUC: 3124 (pmol/L*min) <sup>#</sup>			
			M	10			26				18		30	16	120 min: AUC: 2612 (pmol/L*min) <sup>#</sup>			
		IGT ( <i>n</i> = 525), 3 subgroups <sup>#</sup>	F	11		29					22		30	18	120 min: AUC: 3029 (pmol/L*min) <sup>#</sup>			
		i-IFG (BMI: 27.7 kg/m <sup>2</sup> )																
			M	10			25					17		30	15	120 min: AUC: 2479 (pmol/L*min) <sup>#</sup>		
		i-IGT (BMI: 27.4 kg/m <sup>2</sup> )	F	11			31					22		30	20	120 min: AUC: 3131 (pmol/L*min) <sup>#</sup>		
			M	11			28					18		30	17	120 min: AUC: 2680 (pmol/L*min) <sup>#</sup>		
		IFG&IGT (BMI: 28.8 kg/m <sup>2</sup> )	F	10			26					18		30	16	120 min: AUC: 2591 (pmol/L*min) <sup>#</sup>		
			M	10			25					16		30	15	120 min: AUC: 2466 (pmol/L*min) <sup>#</sup>		
T2DM ( <i>n</i> = 163, BMI: 29.7 kg/m <sup>2</sup> ) <sup>#</sup>	F	9			30					18		30	21	120 min: AUC: 2849 (pmol/L*min) <sup>#</sup>				
	M	11			27					16		30	16	120 min: AUC: 2582 (pmol/L*min) <sup>#</sup>				
Simon et al. 2015 [43] <i>n</i> = 21	RIA <sup>2</sup>	NW-NGT ( <i>n</i> = 11, BMI: 23.6 kg/m <sup>2</sup> ) <sup>#</sup>	6	14		17	21			22	21	22	14	60	16	n.a.	↓ GLP-1 response in OW-NGT compared with NW-NGT	
		OW-NGT ( <i>n</i> = 10, BMI: 35.5 kg/m <sup>2</sup> ) <sup>#</sup>	7	13		18	15			15	14	12	8	20	11			
Wang et al. 2016 [46] <i>n</i> = 80	ELISA (Westang) <sup>3</sup>	NGT ( <i>n</i> = 23, BMI: 25.6 kg/m <sup>2</sup> )		19				65		54		48	37	30	46	180 min: AUC: 192 (pmol/L*min)	- ↓ fasting values in T2DM compared with NGT	

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TABLE 1 (continued)

Author, (y), <i>n</i>	GLP-1 assay	Participant characteristics	GLP-1 values (pmol/L) at time points (min)											TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC	Results
			0	10	15	20	30	40	45	60	90	120	180				
(Han Chinese adults)		IGT ( <i>n</i> = 22, BMI: 26.0 kg/m <sup>2</sup> )	16				60			50		45	21	30	44	180 min: AUC: 182 (pmol/L*min)	- ↓ peak values and AUC in T2DM compared with NGT/ IGT - no significant differences between NGT/ IGT ↓ AUC in OW
		T2DM ( <i>n</i> = 35, BMI: 26.5 kg/m <sup>2</sup> )	15				42			38		35	26	30	27	180 min: AUC: 129 (pmol/L*min)	
Chia et al. 2017 [52] <i>n</i> = 40	ELISA (Alpco) <sup>4</sup>	NW ( <i>n</i> = 20, BMI: 23.6 kg/m <sup>2</sup> )	3			14		11		10		9		20	11	120 min: AUC: 1150 (pmol/L*min) <sup>#</sup>	
		OW ( <i>n</i> = 20, BMI: 35.6 kg/m <sup>2</sup> )	4			11		10		7		5		20	7	120 min: AUC: 831 (pmol/L*min) <sup>#</sup>	
Dybjer et al. 2020 [51] <i>n</i> = 3001	RIA <sub>Linco</sub> <sup>1</sup>	NGT ( <i>n</i> = 2453, BMI: 26.3 kg/m <sup>2</sup> ) <sup>#</sup>	8									18		120	10	n.a.	- ↑ fasting levels in DM compared with NGT - ↓ postprandial levels in DM compared with NGT - ↑ levels at fasting, after 30 min and AUC in T2DM compared with IGT and NGT - ↑ levels at fasting, after 30 min and AUC in IGT compared with NGT
		DM ( <i>n</i> = 548, BMI: 28.7 kg/m <sup>2</sup> ) <sup>#</sup>	9									16		120	7		
Chong et al. 2022 [50] <i>n</i> = 174	ELISA (Millipore) <sup>5</sup>	NGT ( <i>n</i> = 58, BMI: 24 kg/m <sup>2</sup> ) <sup>#</sup>	16				31					24		30	15	120 min: AUC: 3266 (pmol/L*min) <sup>#</sup>	
		IGT ( <i>n</i> = 54, BMI: 26.2 kg/m <sup>2</sup> ) <sup>#</sup>	22				41					25		30	19	120 min: AUC: 3994 (pmol/L*min) <sup>#</sup>	
		T2DM ( <i>n</i> = 62, BMI: 26.7 kg/m <sup>2</sup> ) <sup>#</sup>	27				50					28		30	23	120 min: AUC: 4698 (pmol/L*min) <sup>#</sup>	

GLP-1 concentrations for selected time points of blood sampling, time-to-peak as well as peak (peak concentration – fasting concentration), and—if available—AUC or iAUC values are listed. Under “results,” only significant results are listed. Time point 0 describes fasting concentrations, and time points >0 are reporting postprandial concentrations.

<sup>#</sup>original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups, ↔ no differences of GLP-1 secretion between groups. Supplemental Table 2 shows GLP-1 values for all measured time points. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:

**Abbreviations:** AUC, the area under the curve; CV, coefficient of variation; DM, diabetes mellitus; F, female; GLP-1, glucagon-like peptide 1; IFG, impaired fasting glucose; i-IFG, isolated impaired fasting glucose; IGT, impaired glucose tolerance; i-IGT, isolated impaired glucose tolerance; LOD, limit of detection; M, male; n.a., not available; NGT, normal glucose tolerance; NW, normal weight; OGTT, oral glucose tolerance test; OW, overweight; RIA, radioimmunoassay; TTP, time-to-peak; T2DM, type 2 diabetes mellitus.

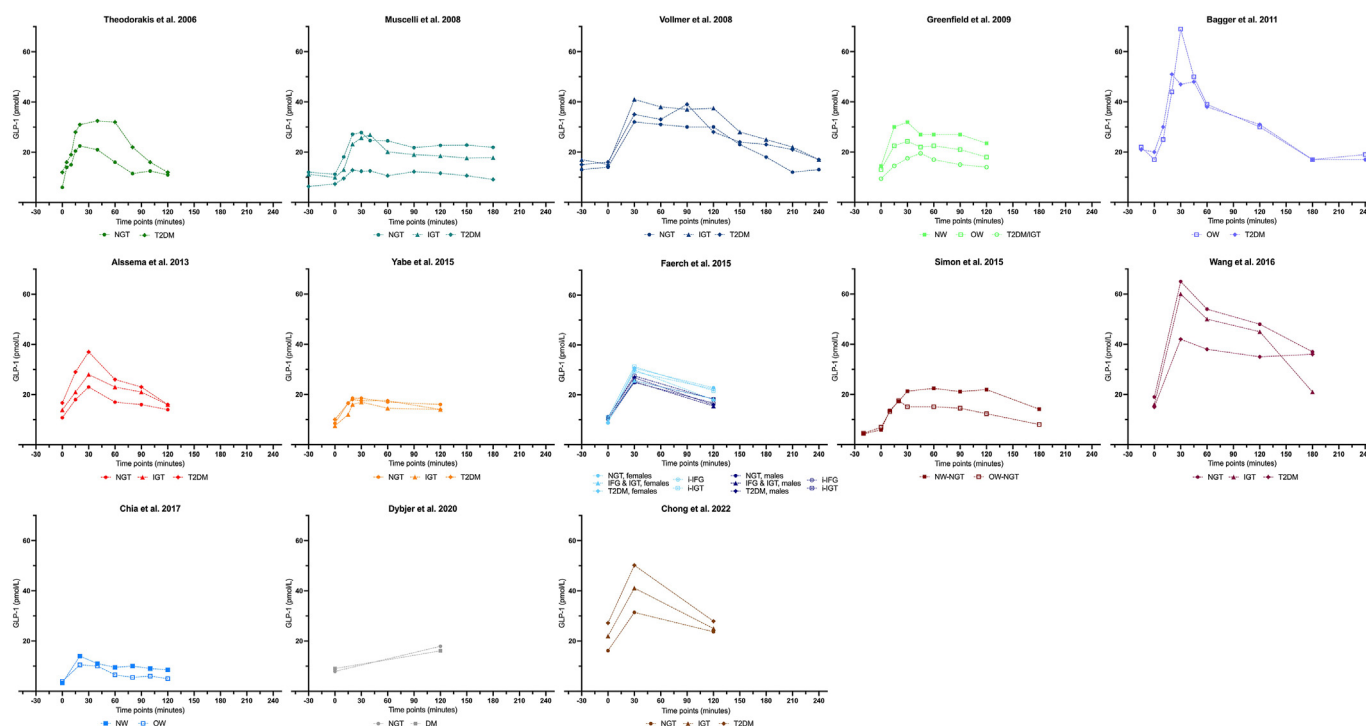
<sup>1</sup> RIA<sub>Linco</sub> (Linco Research), polyclonal antiserum no. 89390, LOD: 3 pM, intra-assay CV: 5%, inter-assay CV: 17%, specificity: 100% for GLP-1 (7–36) and GLP-1 (9–36);

<sup>2</sup> RIA: standardized assay (41), polyclonal antiserum no. 89390, LOD: 1 pM, intra-assay CV: 6%, specificity: 100% for GLP-1 (7–36) 89% for GLP-1 (9–36);

<sup>3</sup> ELISA (Westang Biological Technology), sensitivity: <0.1 pM, intra- and inter-assay CV: <10.3%;

<sup>4</sup> ELISA (Alpco Diagnostics), intra-assay CV: 3.7%–4.7%, inter-assay CV: 6.2–9.5%;

<sup>5</sup> ELISA (EMD Millipore), LOD: 1.5 pM, intra-assay CV: <2% inter-assay CV: <12%.



**FIGURE 1.** Glucagon-like peptide 1 concentrations during oral glucose tolerance tests in different metabolic conditions. Mean fasting and postprandial values of participants with normal glucose tolerance, impaired glucose tolerance, isolated impaired glucose tolerance, impaired fasting glucose or isolated impaired fasting glucose, type 2 diabetes mellitus or diabetes mellitus, normal weight, and overweight in 13 studies [39,42–53].

response after the ingestion of a western-styled breakfast meal consisting of bread with butter, cheese, and jam (424 kcal) in insulin-resistant males when compared with matched nondiabetic controls. Fifteen minutes after meal ingestion, GLP-1 concentrations in the insulin-resistant participants reached 44% of the GLP-1 concentrations of their matched controls. Additionally, the  $iAUC_{30min}$  was 45% lower than that in the insulin-sensitive controls. Furthermore, an association was found between the degree of insulin resistance and impaired GLP-1 response [57]. Toft-Nielsen et al. [38], reported important results after conducting a western-styled challenge breakfast meal test (537 kcal). Although lower AUC and  $iAUC$  values were observed in the T2DM group than in the NGT and IGT groups, higher fasting values were observed in the T2DM group than in the NGT group, whereas there were no significant differences between the three groups. The AUC for the IGT group ranged between those of the NGT and T2DM groups. Furthermore, the AUC in male participants was lower than that in female participants and decreased with increasing BMI [38].

In addition to the studies that showed increased or decreased GLP-1 response in patients with (pre)diabetes, some studies that compared healthy, glucose-tolerant individuals and individuals with IGT/T2DM reported no significant difference in GLP-1 secretion. Likewise, Ryskjær et al. [58] and Vollmer et al. [49] did not find differences in GLP-1 response between NGT/IGT and T2DM groups after consuming a western-styled breakfast meal [58].

A review of 7 studies investigating the MMTT-stimulated GLP-1 response showed that the differences in GLP-1 peak time and concentrations were larger than those in the OGTT studies. This could be due to the heterogeneity of the applied test meals, or also because of the additional protein and fat from the test meals. However, most of the reviewed studies reported an impaired GLP-1 response in patients with (pre)diabetes. Additional research in well characterized, highly

comparable cohorts with different metabolic conditions is needed to evaluate test meal-stimulated GLP-1 response.

### Role of meal composition for GLP-1 secretion

Because human nutrition predominantly consists of meals prepared by combining foods, analyzing the effect of whole meals or meal patterns on GLP-1 secretion, in addition to the OGTT and MMTT, is an important approach. Among other things, meal composition could also influence the results of MMTT or challenge meal studies. In this review, 14 intervention studies compared GLP-1 responses to different liquid or solid tests and challenge meals or foods; see Table 3 [59–71] and Supplemental Table 4. Although for most studies no information on meal duration was provided, the meal durations in the remaining studies were 10–20 min. These studies varied in the methods used to measure the GLP-1 concentrations.

Across all the studies and participants, the maximum postprandial GLP-1 concentrations were reached between 15 [59] and 180 [60–62] min after the ingestion of the test meal.

Adding plant-based foods such as berries [63], virgin olive oil [61], or mushroom powder [64] to the test meals compared with nonfortified test meals resulted in increased postprandial GLP-1 secretion in individuals who were of NW or OW groups, or had IFG. In another study, a vegan test meal increased the postprandial GLP-1 response in patients with T2DM compared with an isoenergetic test meal containing processed meat. Further, the GLP-1 peak concentration was more than twice as high after the vegan test meal, indicating the possible clinical relevance of this acute change. However, similar effects have not been demonstrated in healthy or glucose-tolerant individuals [65]. Another study examining the effect of Scottish oats compared with that of isoenergetic pearl millet porridge on the postprandial GLP-1 response in healthy NW adults showed no differences between the 2 test meals

**TABLE 2**

Food-stimulated GLP-1 response (MMTT/ challenge meals)

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics	GLP-1 values (pmol/L) at time points (min)										TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC	Results
				0	15	30	45	60	90	120	150	180					
Solid meals Rask et al. 2001 [57] <i>n</i> = 33 males	RIA <sup>1</sup>	Western-styled breakfast (10 min) (424 kcal, 49% CH, 38% F, 13% P)	High IS (HIS, <i>n</i> = 11, BMI:: 23.9 kg/m <sup>2</sup> )	11	19	17	14	15	16	15		14	15	8	45 min: 771 (pmol/L*min) <sup>#</sup>	↔ fasting levels, total AUC, iAUC - ↓ 15min values in LIS compared with HIS - ↓ overall and early GLP-1 response (AUC) in LIS compared with HIS - ↓ AUC and iAUC in T2DM compared with NGT (and IGT upon ANOVA correcting for BMI: and sex) - ↑ fasting values in T2DM compared with NGT; ↔ upon ANOVA	
			Medium IS (MIS, <i>n</i> = 11, BMI:: 26.4 kg/m <sup>2</sup> )	8	13	16	14	15	15	15		13	30	8	n.a.		
			Low IS (LIS, <i>n</i> = 11, BMI:: 30.4 kg/m <sup>2</sup> )	6	8	14	11	10	11	13		10	30	8	45 min: 482 (pmol/L*min) <sup>#</sup>		
Toft-Nielsen et al. 2001 [38] <i>n</i> = 102	RIA <sup>1</sup>	Western-styled breakfast (10-15 min) (537 kcal, 41% CH, 42% F, 17% P)	NGT ( <i>n</i> = 33, BMI:: 29.6 kg/m <sup>2</sup> )	5		14		18	18	16		11	60	80	13	240 min: AUC: 3101 iAUC: 1927 (pmol/L*min) <sup>#</sup>	↔ AUC, iAUC
			IGT ( <i>n</i> = 15, BMI:: 35 kg/m <sup>2</sup> )	5		13		16	14	13		10	60	11	240 min: AUC: 2765 iAUC: 1587 (pmol/L*min) <sup>#</sup>		
			T2DM ( <i>n</i> = 54, BMI:: 30.2 kg/m <sup>2</sup> )	7		13		14	12	11		9	60	7	240 min: AUC: 2482 iAUC: 907 (pmol/L*min) <sup>#</sup>		
Vilsbøll et al. 2003 [56] <i>n</i> = 24	RIA <sup>1</sup>	Western-styled breakfast (10 min) (48% CH, 33% F, 19% P) Small (S) (260 kcal) Large (L) (520 kcal)	NGT-NW ( <i>n</i> = 8, BMI:: 22.5 kg/m <sup>2</sup> )	S	14	23	31	30	31	25	21	18	17	60	17	180 min: 3336 (pmol/L* min) <sup>#</sup>	- ↓ AUC, iAUC in T2DM compared with matched NGT (small and large meal) - ↓ late phase values in T2DM compared with matched NGT (small meal)
				L	18	21	35	31	30	33	30	28	25	30	17	180 min: 4197 (pmol/L* min) <sup>#</sup>	
			NGT-OW ( <i>n</i> = 8, BMI:: 32.5 kg/m <sup>2</sup> )	S	17	26	36	33	34	33	27	27	26	30	19	180 min: 4301 (pmol/L* min) <sup>#</sup>	
				L	17	29	42	40	40	37	36	32	29	30	25	180 min: 5030 (pmol/L* min) <sup>#</sup>	
			T2DM ( <i>n</i> = 8, BMI:: 32.1 kg/m <sup>2</sup> )	S	18	19	29	30	27	20	19	17	18	45	12	180 min: (pmol/L* min) <sup>#</sup>	
				L	18	19	31	32	34	33	30	23	20	60	16	180 min: 4008 (pmol/L* min) <sup>#</sup>	
Ryskjær et al. 2006 [58] <i>n</i> = 16	RIA <sup>1</sup>	Western-styled breakfast (15 min) (566 kcal, 47% CH, 34% F, 19% P)	NGT ( <i>n</i> = 8, BMI:: 30.9 kg/m <sup>2</sup> )		20	21	28	28	29	31	28	27	26	90	11	180 min: AUC: 4877 iAUC: 1296 (pmol/L* min) <sup>#</sup>	↔ AUC, iAUC
			T2DM ( <i>n</i> = 8, BMI:: 33 kg/m <sup>2</sup> )		23	27	38	39	34	35	33	31	33	45	16	180 min: AUC: 5950 iAUC: 1735 (pmol/L* min) <sup>#</sup>	
Vollmer et al. 2008 [49] <i>n</i> = 48	RIA <sup>1</sup>	Western-styled breakfast (15 min) (820 kcal, 44% CH, 43% F, 13% P)	NGT ( <i>n</i> = 14, BMI:: 27.5 kg/m <sup>2</sup> )		14		24		30	33	31	34	29	150	20	n.a.	↔
			IGT ( <i>n</i> = 17, BMI: 29.5 kg/m <sup>2</sup> )		19		35		38	41	34	36	37	90	22		
			T2DM ( <i>n</i> = 17, BMI:: 32.1 kg/m <sup>2</sup> )		14		37		33	37	31	34	29	30	90	23	

(continued on next page)



TABLE 2 (continued)

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics	GLP-1 values (pmol/L) at time points (min)									TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC	Results
				0	15	30	45	60	90	120	150	180				
Alssema et al. 2013 [44] n = 203	RIA <sup>1</sup>	Western-styled breakfast (n.a.) (833 kcal, 36% CH, 52% F, 12% P)	NGT (n = 163, BMI: 26.7 kg/m <sup>2</sup> )	11	14	17		16	18	20		17	120	9	AUC: 17 iAUC: 5.8 (pmol/L per hour) AUC: 20 iAUC: 5.5 (pmol/L per hour) AUC: 20 iAUC: 3 (pmol/L per hour)	- ↓GLP-1 response in T2DM compared with NGT/IGT - ↔ AUC - ↓ iAUC in T2DM compared with NGT/IGT - no differences between NGT/IGT
			IGT (n = 20, BMI:: 28.5 kg/m <sup>2</sup> )	13	15	21		18	22	22		18	90 120	9		
			T2DM (n = 20, BMI:: 33.1 kg/m <sup>2</sup> )	16	18	22		21	21	20		18	30	6		
Solid + liquid meals																
Ruetten et al. 2018 [55] n = 62	RIA (Merck Millipore) <sup>2</sup>	Test meal (10 Min) 237ml Boost (Nestlé) + 1 PowerBar (Nestlé) (470 kcal, 66% CH, 18% F, 16% P)	NGT (n = 23, BMI:: 31.5 kg/m <sup>2</sup> )	5		13		8		9			30	8	120 min: iAUC: 512 (pmol*min/mL) 120 min: iAUC: 384 (pmol*min/mL) 120 min: iAUC: 785 (pmol*min/mL)	-↑ fasting values in T2DM compared with NGT/IGT -↑ iAUC in T2DM compared with NGT/IGT
			IGT (n = 17, BMI:: 35 kg/m <sup>2</sup> )	5		10		9	8			30	5			
			T2DM (n = 22, BMI:: 32.8 kg/m <sup>2</sup> )	9		20		17	12			30	11			

GLP-1 concentrations for selected time points of blood sampling, time-to-peak as well as peak (peak concentration – fasting concentration) and—if available—AUC or iAUC values are listed. Under “results” only significant results are listed. Time point 0 describes fasting concentrations, time points >0 are reporting postprandial concentrations. Under “results” only significant results are listed.

<sup>#</sup>original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups, ↔ no differences of GLP-1 secretion between groups.

Supplemental Table 3 shows GLP-1 values for all measured time points. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:

Abbreviations: AUC, area under the curve; CH, carbohydrate; CV, coefficient of variation; F, fat; GLP-1, glucagon-like peptide 1; HIS, high insulin sensitivity; iAUC: incremental area under the curve; IGT, impaired glucose tolerance; IS, insulin sensitivity; L, large; LIS, low insulin sensitivity; LOD, limit of detection; MIS, medium insulin sensitivity; MMTT, mixed meal tolerance test; n.a., not available; NGT, normal glucose tolerance; NW, normal weight; OW, overweight; P, protein; RIA, radioimmunoassay; S, small; TTP, time-to-peak; T2DM, type 2 diabetes mellitus.

<sup>1</sup> RIA [standardized assay (41)], polyclonal antiserum no. 89390, LOD: 1 pM, intra-assay CV: 6%, specificity: 100% for GLP-1 (7–36) 89% for GLP-1 (9–36);

<sup>2</sup> RIA (Merck Millipore), sensitivity: 3 pM, specificity: 100% for GLP-1 (7–36) and GLP-1 (9–36), intra-assay CV: 22–36%, inter-assay CV: 10–23%.

**TABLE 3**  
GLP-1 response and meal composition

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics		GLP-1 values (pmol/L) at time points (min)									TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/ iAUC	Results
					0	15	30	45	60	90	120	180	240				
Solid meals																	
Rijkeljkhuizen et al. 2010 [69] <i>n</i> = 24	RIA <sup>1</sup>	Test meals (10 min)	NGT ( <i>n</i> = 6,	SCH	5		11		13		14		120	9	120 min: iAUC: 13.5 (pmol/L*h)	↔ absolute values	
RCT cross-over		Small CH-rich meal (SCH, 460 kcal, 66% CH, 18% F, 16% P)	BMI:: 26.9 kg/m <sup>2</sup> )	LCH	7		15		17		22		120	15	120 min: iAUC: 16.8 (pmol/L*h)	- in NGT values still rising after first 2 h, in T2DM stabilized	
				FRM	4		15		13		16		120	12	120 min: iAUC: 19.1 (pmol/L*h)	-↑ iAUC after LCH compared with	
		Large CH-rich meal (LCH, 680 kcal, 66% CH, 18% F, 16% P)	T2DM ( <i>n</i> = 18, BMI:: 28.9 kg/m <sup>2</sup> )	SCH	3		13		15		14		60	12	120 min: iAUC: 18.3 (pmol/L*h)	FRM in T2DM	
				LCH	3		18		19		19		60 120	16	120 min: iAUC: 23.8 (pmol/L*h)		
		Fat-rich meal (FRM, 833 kcal, 36% CH, 52% F, 12% P)		FRM	3		13		12		12		30	10	120 min: iAUC: 13.6 (pmol/L*h)		
Törrönen et al. 2012 [63] <i>n</i> = 12	ELISA (Millipore) <sup>2</sup>	Test meal (n.a.): IG: 35 g sugar + berries (150 g)	NGT (BMI:: 24.3 kg/m <sup>2</sup> )	IG	26	32	34	28	27	26	25		30	8	120 min: AUC: 312 (pmol/L*min) <sup>#</sup>	↑ GLP-1 secretion (overall difference) borderline	
RPCT cross-over		CG: placebo		CG	25	29	30	26	26	26	25		30	5	120 min: AUC: 216 (pmol/L*min) <sup>#</sup> n.a.	significant in IG compared with CG	
Belinova et al. 2014 [65] <i>n</i> = 100	Multiplex immunoanalysis	Test meal (n.a.): VE: Vegan (455 kcal, 52% CH, 37% F, 11% P)	NGT ( <i>n</i> = 50, BMI:: 24.4 kg/m <sup>2</sup> )	VE	3.7		3.9		4		3.8	3.7	60	0.3		↑ postprandial GLP-1 concentration in	
RCT cross-over	xMAP technology <sup>3</sup>	ME: processed meat meal (455 kcal, 27% CH, 52% F, 21% P)	T2DM ( <i>n</i> = 50, BMI:: 33.3 kg/m <sup>2</sup> )	ME	3.6		4.3		4.2		3.9	3.8	30	0.7		T2DM in VE	
				VE	4.5		11		7.5		5	4.5	30	6.5		compared with ME	
				ME	4		4.5		4.7		4.4	4.2	60	0.7			
Carnevale et al. 2017 [61] <i>n</i> = 30	ELISA (Sigma Aldrich) <sup>4</sup>	Test meal (n.a.): (725 kcal, 53-54% CH, 28-30% F, 16-19% P)	IFG (BMI:: 31.3 kg/m <sup>2</sup> ) <sup>#</sup>	IG	2				5		12		120	10	n.a	↑ GLP-1 secretion in IG compared with CG	
RCT cross-over		IG: with CG: without olive oil		CG	2				3		6		120	4			
Alyami et al. 2019 [66] <i>n</i> = 26	ELISA (Millipore) <sup>2</sup>	Breakfast meal (15 min): SOP: Scottish oats porridge (220 kcal, 42 g CH, 4.4 g F)	NGT (BMI:: 23.4 kg/m <sup>2</sup> ) <sup>#</sup>	SOP	27	39	37	29	25	24	22		15	12	120 min: iAUC: 3670 (pmol/L*min) <sup>#</sup>	↔	
RCT cross-over		PMP: Pearl millet porridge (220 kcal, 44 g CH, 3 g F)		PMP	29	35	37	29	24	21	22		30	8	120 min: iAUC: 3467 (pmol/L*min) <sup>#</sup>		
Schönknecht et al. 2020 [60] <i>n</i> = 60	RIA <sup>1</sup>	Breakfast challenge meal (20 min): WDHF: Western diet high-fat (1010 kcal, 37% CH, 53% F, 10% P)	OW (BMI:: 30.9 kg/m <sup>2</sup> ) <sup>#</sup>	WDHF	29				44		44	30	37	60 120	15	300 min: iAUC: 46 (pmol/L*h) <sup>#</sup>	↔ fasting/postprandial values, iAUC
RCT cross-over		WDHC: Western diet high-fat (1010 kcal, 37% CH, 53% F, 10% P)		WDHC	30				44		46	41	37	120	16	300 min: iAUC: 44 (pmol/L*h) <sup>#</sup>	
		WDHC: Western diet high-fat (1010 kcal, 37% CH, 53% F, 10% P)		MED	29				44		44	40	38	60 120	15	300 min: iAUC: 45 (pmol/L*h) <sup>#</sup>	

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TABLE 3 (continued)

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics		GLP-1 values (pmol/L) at time points (min)										TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/ iAUC	Results
					0	15	30	45	60	90	120	180	240					
Di Mauro et al. 2021 [68] n = 12 RCT cross-over	ELISA (Millipore) <sup>2</sup>	diet high-CH (1013 kcal, 58% CH, 31% F, 10% P) MED: Mediterranean Diet (1012 kcal, 53% CH, 36% F, 10% P)	T2DM (BMI:: 34.4 kg/m <sup>2</sup> )	MED	13		18		17	17	17	15		30	5	210 min: AUC: 11359 (pg/mL*min) <sup>#</sup>	- ↑ AUC in MED compared with HFV ↔ iAUC (trend for ↑ in MED)	
		Test meal (n.a.): MED: Mediterranean diet (665 kcal, 32% CH, 45% F, 23% P)			12		16		14	15	13	13		30	4	210 min: AUC: 9576 (pg/mL*min) <sup>#</sup>		
		HVF: High-fiber Vegetarian diet (704 kcal, 78% CH, 8% F, 15% P)																
Muangchan et al. 2021 [62] n = 6 RCT cross-over	ELISA (Millipore) <sup>2</sup>	Test meal (n.a.): 100 g steamed rice with microwaved labeled egg + water	NW (BMI:: 21.5 kg/m <sup>2</sup> )	IG	38	39	37		35		43	21		120	5	180 min: iAUC: 7094 (pmol/L*min)	- ↔ iAUC - trend for ↑ values in IG after 30 and 60 min	
		IG: Riceberry rice (370 kcal, 75.5 g CH, 3.6 g F, 8.6 g P, 4.1 g fiber) CG: white rice (350 kcal, 79.4 g CH, 1.2 g F, 5.7 g P, 1.7 g fiber)		CG	32	31	28		27		33	38		180	6	180 min: iAUC: 5687 (pmol/L*min)		
Dicks et al. 2022 [64] n = 22 RCT cross-over	RIA <sup>1</sup>	Test meal (15 min): IG: Enriched with 20 g powder of oyster mushroom (456 kcal, 67.9 g CH, 21.8 g F, 7.1 g P)	IGT (BMI:: 31.3 kg/m <sup>2</sup> )	IG	10	18	22	25	29	29	27	18	11	60 90	19	240 min: AUC: 5380 (pmol/L*min)	- ↑ concentration at 180 min in IG compared with CG - ↑ AUC in IG compared with CG	
		CG: without enrichment (403 kcal, 52.5 g CH, 21.5 g F, 5.0 g P)		CG	9	17	21	25	28	25	23	13	9	60	19	240 min: AUC: 4612 (pmol/L*min)		
Bajka et al. 2023 [71] n = 20 RCT cross-over	Electrochemiluminescent multiplexed assay (Mesoscale Discovery) <sup>5</sup>	Test meal (n.a.): bread with jam + water	NW (BMI: ~. 23.5 kg/m <sup>2</sup> )	IG1	0	15	29	25	29	25	20	10	6	30 60	29	120 min: iAUC: 2825 (pmol/L*min) <sup>#</sup>	- ↑ iAUC and postprandial values in IGs compared with CG, especially during late postprandial period. IG2 lead to higher secretion than IG1 - ↔ maximum values, but peaks	
		IG1: wheat bread with 30% cellular chickpea powder (360 kcal, 48.3 g CH, 5.6 g F, 17.7 g P, 6.2 g fiber)		IG2	0	12	26	25	27	33	31	22	15	90	33	120 min: iAUC: 3051 (pmol/L*min) <sup>#</sup>		
		IG2: wheat bread		CG	0	14	25	21	17	15	11	3	2	30	25	120 min: iAUC: 1966 (pmol/L*min) <sup>#</sup>		

(continued on next page)

TABLE 3 (continued)

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics	GLP-1 values (pmol/L) at time points (min)									TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/ iAUC	Results		
				0	15	30	45	60	90	120	180	240						
		with 60% cellular chickpea powder (435 kcal, 48.2 g CH, 8.8 g F, 27.2 g P, 10.7 g fiber) CG: wheat bread (310 kcal, 48.1 g CH, 3.3 g F, 12.9 g P, 2.6 g fiber)															were reached ~ 40 min later in IG2	
Nakamura et al. 2023 [67] <i>n</i> = 17 RCT cross-over	ELISA (Yanaihara Institute Inc.) <sup>6</sup>	Test meal (n.a.): IG: 150 g cooked OIST rice (222 kcal, 45 g CH, 2.1 g F, 5.9 g P, 7.1 g resistant starch)	T2DM (BMI:: 25.9 kg/m <sup>2</sup> )	IG	13		18		15		14		15	30	5	240 min: AUC: 3964 iAUC: 505 (pmol/L*min) <sup>#</sup>	↔ (i)AUC	
		CG: 150 g cooked white rice (210 kcal, 48.5 g CH, 0.5 g F, 3 g P, 1.4 g resistant starch)		CG	14		20		19		17		17	30	6	240 min: AUC: 3970 iAUC: 608 (pmol/L*min) <sup>#</sup>		
Liquid (+ solid) meals																		
Lamiquiz-Moneo et al. 2022 [59] <i>n</i> = 10 RCT cross-over	Human Metabolic Hormone Magnetic Bead Panel (Merck) <sup>7</sup>	Test drinks: Isoglucidic interventions (25 g CH) (n.a.)	NW (BMI:: 23.4 kg/m <sup>2</sup> )	IG1	51	56	46	38	38	42	21			15	5	120 min: AUC: 17402	- ↑ AUC in all IGs compared with CG	
		IG1: Regular alcohol-free beer (AFB)		IG2	52	52	45	40	37	41	43			0	15	0	120 min: AUC: 16929	- ↔ iAUC
		IG2: CH-modified AFB + isomaltulose (2.5 g/100 ml) + resistant maltodextrin (0.8 g/100 ml)		IG3	50	49	40	40	38	41	42			0		-1	120 min: AUC: 16633	- ↔ maximum increase over baseline value
		IG3: CH-modified AFB + resistant maltodextrin (2.0 g/100 ml) CG: glucose (25 g CH)		CG	47	51	40	32	29	29	31			15	4		120 min: AUC: 13580	
Lamiquiz-Moneo et al. 2022 [59] <i>n</i> = 20 RCT cross-over	Human Metabolic Hormone Magnetic Bead Panel (Merck) <sup>7</sup>	Test meals + drinks: Isoglucidic interventions (64.3 g CH) (n.a.)	NW (BMI:: 24.4 kg/m <sup>2</sup> )	IG1	59	67	59	53	50	48	46			15	8	120 min: AUC: 20,813	- ↑ AUC in all IGs compared with CG	
		50 g CH from white bread + 14.3 g CH from IG1: AFB		IG2	57	58	55	53	48	44	42			15	1	120 min: AUC: 18,338	- ↑ AUC in IG1 compared with IG2	
				IG3	49	57	50	46	44	46	40			15	8	120 min: AUC: 19,560	- ↔ iAUC	
				IG4	50	60	59	53	50	42	39			15	10	120 min: AUC: 19,443	- ↔ maximum increase over baseline value	

(continued on next page)

TABLE 3 (continued)

Author, (y), n	GLP-1 assay	Test meal (Duration, nutrient composition)	Participant characteristics		GLP-1 values (pmol/L) at time points (min)								TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/ iAUC	Results	
					0	15	30	45	60	90	120	180					240
Smith et al. 2023 [70] n = 18 RCT cross-over	ELISA (Millipore) <sup>2</sup>	IG2: CH-modified AFB + isomaltulose (2.5 g/ 100 mL) + resistant maltodextrin (0.8 g /100 mL)	T2DM (BMI:: 32.7 kg/m <sup>2</sup> )	CG	45	49	48	44	40	36	36			15	4	120 min: AUC: 16,286	↑ iAUC and postprandial values in IG compared with CG
		IG3: CH-modified AFB + resistant maltodextrin															
		IG4: Extra white bread + water															
		CG: + water (50 g CH)															
		Test meal (15 min): cereal + milk (387 kcal, 58% CH, 27% F, 15% P)		IG	47	58	62	57	55	51	45	38	35	30	15	240 min: iAUC: 14.6 (pmol/ L*min) <sup>#</sup>	
		IG: test meal + pre-meal whey protein drink (100 kcal, 15.6 g P)		CG	35	44	46	46	43	39	33	29	31	30 45	11	240 min: iAUC: 4.4 (pmol/ L*min) <sup>#</sup>	
		CG: test meal + pre-meal placebo shot (35 kcal, <.1 g P)															

GLP-1 concentrations for selected time points of blood sampling, time-to-peak as well as  $\Delta$  peak (peak concentration – fasting concentration) and —if available—AUC or iAUC values are listed. Under “results” only significant results are listed. Time point 0 describes fasting concentrations, time points >0 are reporting postprandial concentrations.

<sup>#</sup>original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups, ↔ no differences of GLP-1 secretion between groups.

Supplemental Table 4 shows GLP-1 values for all measured time points. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:

Abbreviations: AFB, alcohol-free beer; approx., approximately; AUC, area under the curve; CH, carbohydrates; CG, control group; CV, coefficient of variation; F, fat; FRM, fat-rich meal; GLP-1, glucagon-like peptide 1; HFV, high-fiber vegetarian diet; iAUC, incremental area under the curve; IFG, impaired fasting glucose; IG, intervention group; IGT, impaired glucose tolerance; LCH, large carbohydrate-rich meal; LOD, limit of detection; ME, meat meal; MED, Mediterranean diet; n.a., not available; NGT, normal glucose tolerance; NW, normal weight, OW, overweight; P, protein; PMP, pearl millet porridge; RIA, radioimmunoassay; RPCT, randomized placebo-controlled trial; SCH, small carbohydrate-rich meal; SOP, Scottish oats porridge; TTP, time-to-peak; T2DM, type 2 diabetes mellitus; VE, vegan meal; WDHC, western diet high-carbohydrate; WDHF, western diet high-fat.

<sup>1</sup> RIA [standardized assay (41)], polyclonal antiserum no. 89390, LOD: 1 pM, intra-assay CV: 6%, specificity: 100% for GLP-1 (7–36) 89% for GLP-1 (9–36);

<sup>2</sup> ELISA (Merck Millipore), LOD: 1.5 pM, intra-assay CV: < 5%, inter-assay CV: < 12%;

<sup>3</sup> Multiplex immunoanalysis xMAP technology, MILLIPEX MAP Human Gut Hormone Panel (Millipore), sensitivity: 13.7 pg/mL;

<sup>4</sup> ELISA (Arbor Assay, Sigma Aldrich), sensitivity: 1.5 pM, intra-assay CV: 1%–2%, inter-assay CV: < 12%;

<sup>5</sup> Electrochemilumin-escent multiplexed assay (Mesoscale Discovery), n.a.;

<sup>6</sup> ELISA (YK 161, Yanaihara Institute Inc.), sensitivity: 1.5 pM, intra-assay CV: 2%–5.4%, inter-assay CV: 2.2%–3.8%, cross-reactivity: 100% for GLP-1 (7–36) and for GLP-1 (9–36);

<sup>7</sup> Human Metabolic Hormone Magnetic Bead Panel MILLIPEX MAP Kits (Cat. # HMHEMAG-34K, Merck), sensitivity: 7.3 pg/mL, intra-assay CV: < 10%, inter-assay CV: < 15%.

**TABLE 4**

Glucose- or food-stimulated GLP-1 secretion after short-, mid-, and long-term dietary interventions

Author, (y), n	GLP-1 assay	Intervention Participant characteristics		GLP-1 values (pmol/L) at time points (min)								TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC (pmol/L * min)	Results
				0	30	60	90	120	150	180					
Glucose-stimulated GLP-1 secretion (OGTT) before and after dietary intervention															
Otten et al. 2019 [72] <i>n</i> = 70 RCT	RIA <sup>1</sup>	2-y intervention: Paleo diet (PD) Healthy Nordic Diet (ND) (slight energy reduction) NGT (BMI: 32.3 kg/m <sup>2</sup> ) females	ND <sup>#</sup>	0 mo	10	18	20	18	17		60	10	120 min: AUC: 2424 iAUC: 1084	- ↑ AUC, iAUC in PD and ND compared with baseline - ↑ fasting values in ND compared with baseline	
				6 mo	10	21	21	19	19		30 60	11	120 min: AUC: 2769 iAUC: 1449		
				24 mo	12	27	26	24	22		30	15	120 min: AUC: 2826 iAUC: 1572		
			PD <sup>#</sup>	0 mo	11	23	21	22	20		30	12	120 min: AUC: 2113 iAUC: 933		
				6 mo	11	25	26	25	24		60	15	120 min: AUC: 2287 iAUC: 1036		
				24 mo	11	26	26	26	24		30 60 90	15	120 min: AUC: 2907 iAUC: 1488		
Stentz et al. 2021 [74] <i>n</i> = 24 RCT	Human Metabolic Hormone Magnetic Bead Panel (Merck) <sup>2</sup>	6-mo intervention: Calorie restricted diets (-500 kcal) High-Protein Diet (HP, 40% CH, 30% F, 30% P) High-Carbohydrate Diet (HC, 55% CH, 30% F, 15% P) OW-IGT (BMI: 39.0 kg/m <sup>2</sup> )	HP  HC	0 mo 6 mo 0 mo 6 mo	13 17 15 15	68 85 67 67	44 56 41 48	30 38 29 24	27 29 24 24		30 30 30 30	55 68 52 52	n.a.	↑ AUC in HP compared with HC	
Food-stimulated GLP-1 secretion (test meal) before and after dietary intervention															
Samkani et al. 2018 [78] <i>n</i> = 16 RCT cross-over	RIA <sup>1</sup>	2-d intervention: High-CH (HC, 54% CH, 30% F, 16% P) CH-reduced high-protein (CRHP, 31% CH, 40% F, 29% P) Breakfast test meal on day 2 T2DM (BMI:: 30 kg/m <sup>2</sup> )	HC Day 2 CRHP Day 2		11  11	24  18	30  28	26  30	26  34	28  32	25  28	60  120	19  23	n.a.	- ↑ postprandial value (120 min) in CRHP compared with HC - ↔ netAUC
Samkani et al. 2018 [77] <i>n</i> = 14 RCT cross-over	RIA <sup>1</sup>	2-d intervention: HC (54% CH, 30% F, 16% P)	HC Day 2		0  0	11  9	12  14	12  15	16  20	14  20	13  18	120 150	16 20	n.a.	↑ postprandial/peak, netAUC

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TABLE 4 (continued)

Author, (y), n	GLP-1 assay	Intervention Participant characteristics		GLP-1 values (pmol/L) at time points (min)								TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC/iAUC (pmol/L * min)	Results	
				0	30	60	90	120	150	180						
Fuglsang-Nielsen et al. 2021 [76] <i>n</i> = 73 RCT	RIA <sup>1</sup>	CRHP (31% CH, 40% F 29% P) Breakfast test meal on day 2 NW to OW (BMI:: 32 kg/m <sup>2</sup> )	CRHP Day 2												values in CRHP compared with HC	
		12 wks intervention: Whey Protein (WP, 60 g/d) or Maltodextrin (MD, 60 g/d) combined with High-Fiber (HF, 30 g/d) or Low-Fiber diet (LF, 10 g/d)	WP-HF	0 wk	19.3 <sup>#</sup>								360 min: iAUC: 6143 <sup>#</sup>	↔ fasting values, iAUC		
				12 wks	20.2 <sup>#</sup>								360 min: iAUC: 3791 <sup>#</sup>			
			WP-LF	0 wk	21.5 <sup>#</sup>								360 min: iAUC: 4174 <sup>#</sup>			
				12 wks	19.6 <sup>#</sup>								360 min: iAUC: 4264 <sup>#</sup>			
			MD-HF	0 wk	21.2 <sup>#</sup>								360 min: iAUC: 3896 <sup>#</sup>			
				12 wks	21.1 <sup>#</sup>								360 min: iAUC: 4676 <sup>#</sup>			
			MD-LF	0 wk	21 <sup>#</sup>								360 min: iAUC: 3471 <sup>#</sup>			
			12 wks	20.7 <sup>#</sup>								360 min: iAUC: 3062 <sup>#</sup>				
Oliveira et al. 2022 [75] <i>n</i> = 43 RCT cross-over	V-PLEX (Meso Scale) <sup>3</sup>	32-h intervention: IG: High-protein total diet replacement (35% CH, 25% F, 40% P) CG: (55% CH, 30% F, 15% P) Lunch test meal on day 1 NW (BMI:: 22.0 kg/m <sup>2</sup> )	IG <sup>#</sup>	Day 1	1.6				4.2			120	2.6	n.a.	↑ postprandial values in IG compared with CG on day 1	
				Day 2	1.2											
		CG <sup>#</sup>	Day 1	1.6			2.6			120	1					
			Day 2	1.5												
				Day 2	6.7 <sup>#</sup>	12	10	9	8	10	9	30	5.3		180 min: AUC: 440	↑ fasting values in CG compared with IG on day 2

GLP-1 concentrations for selected time points of blood sampling, time-to-peak as well as peak (peak concentration – fasting concentration), and —if available—AUC or iAUC values are listed. Under “results,” only significant results are listed. Time point 0 describes fasting concentrations, and time points >0 are reporting postprandial concentrations. Under “results,” only significant results are listed.

<sup>#</sup>original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups, ↔ no differences of GLP-1 secretion between groups.

Supplemental Table 5 shows GLP-1 values for all measured time points. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:

Abbreviations: AUC, area under the curve; CH, carbohydrates; CG, control group; CRHP, carbohydrate-reduced-high-protein; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; F, fat; GLP-1, glucagon-like peptide 1; HC, high-carbohydrate; HF, high fiber; HP, high protein; iAUC, incremental area under the curve; iFG, impaired fasting glucose; IG, intervention group; IGT, impaired glucose tolerance; LF, low fiber; LOD, limit of detection; MD, maltodextrin; min, minutes; n.a., not available; ND, healthy nordic diet; NGT, normal glucose tolerance; NW, normal weight, OW, overweight; P, protein; PD, paleo diet; RCT, randomized controlled trial; RIA, radioimmunoassay; RPCT, randomized placebo-controlled trial; RT, randomized trial; TTP, time-to-peak; T2DM, type 2 diabetes mellitus; WP, whey protein.

<sup>1</sup> RIA [standardized assay (41)], polyclonal antiserum no. 89390, LOD: 1 pM, intra-assay CV: 6%, specificity: 100% for GLP-1 (7–36) 89% for GLP-1 (9–36);

<sup>2</sup> Human Metabolic Hormone Magnetic Bead Panel MILLIPLEX MAP Kits (Cat. # HMMHAG-34K, Merck), sensitivity: 7.3 pg/mL, intra-assay CV: < 10%, inter-assay CV: < 15%.

<sup>3</sup> Electro-chemiluminescence V-PLEX (Meso Scale Discovery), specificity: 0.017 pM.

**TABLE 5**  
Fasting GLP-1 values before and after dietary intervention

Author, (y), n	GLP-1 assay	Intervention Participant characteristics	Fasting GLP-1 values (pmol/L)		Δ	Results
			Baseline	Endline		
Ohlsson et al. 2018 [79] n = 30	Bio-Plex Pro Human Diabetes 10- plex panel (Bio-Rad Laboratories) <sup>1</sup>	12 wks Okinawa-based ND (slight energy reduction) T2DM (BMI: 29.9 kg/m <sup>2</sup> )	0.81 <sup>#</sup>	0.54 <sup>#</sup>	-0.27	↓ fasting values compared with baseline
Arjmand et al. 2022 [73] n = 37 RCT	ELISA (Bioassay Technology Laboratory) <sup>2</sup>	12 wks Calorie restricted MIND diet (n = 22) vs. hypocaloric diet (n = 15) (1500 kcal/day, 50%–55% CH, 30% F, 15%–20% P) OW (BMI: 32 kg/m <sup>2</sup> )	MIND diet 12.8 <sup>#</sup> Hypocaloric diet 8.8 <sup>#</sup>	14.7 <sup>#</sup> 7.4 <sup>#</sup>	1.9 -1.4	↑ fasting values after the MIND diet compared with baseline and hypocaloric diet

Fasting GLP-1 concentrations as well as Δ (endline value – baseline value) before and after dietary intervention are listed. Under “results” only significant results are listed.  
<sup>#</sup> original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions.

Abbreviations: CH, carbohydrates; CV, coefficient of variation; F, fat; GLP-1, glucagon-like peptide 1; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; ND, healthy Nordic diet; OW, overweight; P, protein; RCT, randomized controlled trial; T2DM: type 2 diabetes mellitus.

<sup>1</sup> n.a.;  
<sup>2</sup> sensitivity: 1.3 pM; intra-assay CV: 2.8%–5.2%.

[66]. In addition, a comparison of two test meals with either white rice or riceberry rice (rich in antioxidant bioactive compounds and high in protein and fiber) in 6 healthy men did not reveal significant differences in postprandial GLP-1 secretion, whereas there was a slight trend for higher values after consuming riceberry rice [62]. Moreover, in 17 participants with T2DM, a test meal with a newly developed rice variety rich in resistant starch (OIST rice) did not lead to higher GLP-1 AUC or iAUC values than a control meal of regular white rice [67].

When investigating the impact of 3 isocaloric test meals representing 3 different dietary patterns (high-fat western diet, high-carbohydrate western diet, and Mediterranean diet) on 60 participants who were OW, no meal-induced differences in postprandial GLP-1 values were found [60]. In contrast to these results, a recent study of 12 individuals with T2DM found that a Mediterranean test meal led to ~20% higher GLP-1 AUC<sub>210min</sub> than a high-fiber vegetarian test meal. However, when expressed as the iAUC, the difference was not statistically significant [68]. Rijkkelijkhuizen et al. [69] investigated the GLP-1 response after a test meal with a small (460 kcal) and large carbohydrate-rich challenge meal (680 kcal) or a fat-rich meal (833 kcal) in adults with NGT and T2DM. There were no differences in the GLP-1 response (absolute values) detected between both the groups; however, in individuals with NGT, postprandial GLP-1 concentrations kept increasing even 2 h after the meal, whereas in individuals with T2DM, the concentrations returned to baseline levels. Moreover, a large carbohydrate-rich meal caused a ~30% higher iAUC when compared with the fat-rich meal only in adults with T2DM.

A study focusing on the macronutrient composition of test meals found that a meal tolerance test with a liquid pre-meal whey protein shot led to an augmented postprandial GLP-1 response when compared with a placebo shot in 18 patients with T2DM [70]. Bajka et al. [71] found that higher amounts of cellular chickpea flour (60% compared with 30%; meaning higher amounts of protein, fiber, and fat content) led to increased GLP-1 secretion, especially in the late postprandial period in 20 healthy participants. Results on the effect of carbohydrate composition on GLP-1 secretion are discordant. Lamiquiz-Moneo et al. [59] investigated the effects of a liquid (plus solid) test meal and found higher GLP-1 AUCs in NW individuals after a single intake of 3 different complex carbohydrate-containing drinks (regular alcohol-free beer, carbohydrate-modified alcohol-free beer + isomaltulose + resistant maltodextrin, or carbohydrate-modified alcohol-free beer + resistant maltodextrin) compared with consuming an isoglycemic glucose-based control beverage, with no differences between intervention groups. However, when combining the different drinks with white bread, significant differences in the AUC between the intervention groups were observed, in addition to a difference from the control group. The iAUCs and maximum increase in GLP-1 concentrations did not differ significantly between the groups in the 2 studies [59].

After reviewing 14 studies that used single-test meals, we found the results to be inconclusive. However, the results suggest that higher fiber and protein content might substantially increase GLP-1 secretion, with the potential to evoke metabolic alterations.

**GLP-1 secretion after short-, mid-, and long-term dietary interventions**

To date, evidence from controlled human intervention studies investigating the short-term, mid-term or long-term dietary effects on GLP-1 secretion is rare. In this review, fasting and postprandial GLP-1 secretion in humans and controlled intervention studies investigating the effect of short-term to long-term dietary interventions on glucose (OGTT) or food-stimulated (MMTT test or challenge meals) were

examined (see Table 4 for studies assessing dietary intervention effects on glucose- or food-stimulated GLP-1 secretion, Table 5 for studies assessing effects on fasting levels [72–79] and Supplemental Table 5 for GLP-1 concentrations measured at all time points). Different assays were used to measure GLP-1 concentrations in these studies.

In a randomized controlled trial (RCT), the effects of a 2-y paleo compared with healthy Nordic diet in 70 healthy NW females on glucose-stimulated GLP-1 secretion were examined. Here, the Paleo diet was characterized by higher protein and fat content and lower carbohydrate content than the healthy Nordic diet, which was based on the Nordic Nutrition Recommendations. In both groups, iAUCs of GLP-1 after OGTT increased significantly in the Paleolithic group by 45% after 24 mo and in the Nordic group by 59%. Fasting GLP-1 concentrations increased only in the Nordic group. Participants in the Paleolithic group lost on average 10% of their body weight in 24 mo (11% in the first 6 mo), and females in the Nordic group lost 6%. The increase in postprandial GLP-1 concentrations was not associated with the macronutrient composition of the diet but with weight loss. However, even after 6 mo, when body weight remained stable, the postprandial GLP-1 concentrations increased [72]. Similar results were shown in a 12-wk human intervention study comparing a calorie-restricted Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet with a hypocaloric control diet. In 37 women who were OW, a significant increase in fasting GLP-1 concentrations was observed only after the MIND diet. In both groups, a significant reduction in BMI and fat mass was seen, and this decrease was greater in the MIND-diet group. The MIND diet mainly consists of green leafy vegetables, legumes, berries, nuts, fish, poultry, and olive oil, and is similar to the Nordic Diet [73]. Furthermore, in participants who were OW or had IGT, a high-protein diet (40% carbohydrates, 30% fat, and 30% protein) resulted in greater postprandial GLP-1 secretion both during OGTT and MMTT when compared with a high-carbohydrate (HC) diet (55% carbohydrates, 30% fat, and 15% protein). Importantly, the drop-out rate within this study was 36%, which might weaken the findings [74]. This is in line with results from a 32-h RCT in which a high-protein total diet replacement (35% carbohydrates, 25% fat, and 40% protein) led to higher postprandial GLP-1 concentrations 2 h after lunch meal compared with an isocaloric low-protein diet (55% carbohydrates, 30% fat, and 15% protein) [75]. When comparing the effects of maltodextrin (60 g/d) and whey protein (60 g/d) in combination with high-fiber (30 g/d) or low-fiber (30 g/d) in a 12-wk randomized controlled intervention trial in individuals who were OW, no effects on fasting GLP-1 concentrations and meal-stimulated GLP-1 response (iAUC) were observed. In this study, compliance with the study diet was high (88%–94%) and the drop-out rate was low (11%), which might strengthen the findings [76].

Samkani et al. [77] investigated the food-stimulated GLP-1 response in 14 adults who were NW or OW after consuming an HC and carbohydrate-reduced high-protein (CRHP) diet for 2 d. The breakfast meals of the 2 diets also served as the MMTT on day 2. The HC breakfast meal was composed of bread, cheese, ham, eggs, and yogurt, whereas the CRHP breakfast consisted of bread, cheese, jam, eggs, apples, almonds, and milk. The HC lunch consisted of chicken, vegetables, bread, milk, and pasta, whereas the CRHP lunch consisted of chicken, vegetables, chickpeas, feta cheese, and bread. After consumption of the CRHP meal, GLP-1 peak concentration was 17% and net AUC was 27% higher than that after HC meal; both changes were statistically significant. The authors also investigated the effects of similar HC and CRHP breakfast and lunch meals on patients with T2DM. The postprandial concentration at 120 min was significantly

higher in the CRHP group than in the HC group, but there was no significant difference in the GLP-1 net AUC between the 2 test meals [78]. However, the results of a longer-term intervention from an uncontrolled human study contrast these findings. Ohlsson et al. [79] investigated the health effects of a 12-wk Okinawan-based Nordic Diet with moderately low-carbohydrate, high-fat, and high-protein content in 30 individuals with T2DM and showed a significant decrease in fasting GLP-1. The authors attributed the decrease in GLP-1 concentrations to the low-carbohydrate and high-protein content of the diet. In addition, weight loss was observed after 12 wks. Within this study, a comparably high drop-out rate occurred (23%), which might, in combination with the uncontrolled study design, weaken the findings [79].

To summarize, long-term, health-promoting dietary interventions might have the potential to enhance physiologic GLP-1 secretion both in the fasting and postprandial states. In addition, as seen with the ingestion of single-test meals, it seems that increased protein content in the diet may contribute to a sustained enhancement of GLP-1 secretion. Undoubtedly, there is a limited comparative value of 2-d [75,77,78] interventions and interventions with a duration of weeks or months [73, 74,76,79]; however, even very short-term clinical trials can promote an understanding of the underlying mechanisms of diet-induced alterations in GLP-1 secretion, especially as the reported dynamics might recur multiple times of the day after food intake.

### The effect of probiotic, prebiotic, and synbiotic interventions on GLP-1 secretion

To date, the effects of probiotic, prebiotic, and synbiotic interventions on gut hormone secretion in humans have only been examined in a few clinical trials. Moreover, there is high heterogeneity in the methodological approaches regarding the interventions and the GLP-1 assays (see Table 6 for studies assessing intervention effects on glucose- or food-stimulated GLP-1 secretion and Table 7 [80–83] for studies assessing effects on fasting levels and Supplemental Table 6 for GLP-1 concentrations at all time points). We found 2 studies investigating the effects of different probiotic interventions on GLP-1 secretion. Simon et al. [43] showed that a 4-wk probiotic supplementation with *Lactobacillus reuteri* increased GLP-1 concentrations during OGTT by 76% and increased fasting GLP-1 concentrations when compared with the placebo group in 21 glucose-tolerant adults who were either NW or OW. In lean participants, the maximal response to GLP-1 increased in the intervention group. Rondanelli et al. [80] investigated the effect of a 60-d probiotic intervention (500 mg/d *Saccharomyces cerevisiae* variant bouldarii, strain DBVPG 6763 [5.0 × 10<sup>9</sup> colony-forming units (CFU)] in combination with 1000 international units (IU) superoxide dismutase (which is believed to be diminished by an increase of adipose tissue) compared with placebo on fasting GLP-1 concentration in OW individuals. In both groups, the participants followed an energy-restricted diet (~800 kcal of their daily requirement) for the duration of the study. Both groups showed a significant decrease in GLP-1 fasting values but no significant difference was observed between the intervention and placebo groups, which is likely attributable to energy reduction.

Prebiotic interventions were examined in 3 studies. A recent study investigated the effect of a 12-wk prebiotic intervention with 15 g/d wheat bran extract arabinoxylan-oligosaccharide on meal-stimulated GLP-1 secretion in 48 participants with NGT. Compared with the placebo group, the early postprandial GLP-1 response (AUC<sub>0-90min</sub>) was decreased in the prebiotic group after consumption of a solid test meal consisting of 2 slices of white bread, a fried egg, and 250 mL chocolate milk (27% fat, 52% carbohydrates, 19% protein, 412 kcal)

**TABLE 6**  
Glucose- or food-stimulated GLP-1 secretion after pro-, pre-, and synbiotic interventions

Author, (y), n	GLP-1 assay	Intervention Participant characteristics			GLP-1 values (pmol/L) at time points (min)								TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC (pmol/L*min)	Results
					0	20	30	45	60	90	120	180				
Glucose-stimulated GLP-1 secretion (OGTT) before and after interventionrowhead																
Simon et al. 2015 [43] <i>n</i> = 21 RPCT	RIA <sup>1</sup>	4 wks	IG	NW baseline <sup>#</sup>	6	17	24		21	22	22	13	30	18	n.a.	- ↑postprandial values, AUC in IG compared with baseline and CG - ↑ΔAUC in IG compared with CG
		IG: Probiotics (10 <sup>10</sup> b.i.d. <i>L. reuteri</i> SD5865)		NW 4 wks <sup>#</sup>	9	34	37		37	29	5	16	30	28		
			CG	OW baseline <sup>#</sup>	6	16	12		15	14	11	6	20	10		
		CG: Placebo		OW 4 wks <sup>#</sup>	6	17	19		20	15	18	11	60	14		
		NW-NGT ( <i>n</i> = 11, BMI:: 23.6 kg/m <sup>2</sup> )		NW baseline <sup>#</sup>	7	18	20		24	21	23	16	60	17		
				NW 4 wks <sup>#</sup>	8	17	21		20	20	17	12	30	13		
		OW-NGT ( <i>n</i> = 10, BMI:: 35.5 kg/m <sup>2</sup> )		OW baseline <sup>#</sup>	8	19	18		15	15	14	10	20	11		
				OW 4 wks <sup>#</sup>	5	14	14		13	14	13	8	20 30 60	9		
Food-stimulated GLP-1 secretion (test meal) before and after interventionrowhead																
Roshanravan et al. 2017 [23] <i>n</i> = 60 RPCT	ELISA (ZellBio GmbH, Berlin, Germany) <sup>2</sup>	45 d	A	Baseline						27		n.a.	n.a.	n.a.	↑ postprandial values in A + C compared with D	
		Prebiotic supplements		45 d						32						
		A) sodium butyrate	B	Baseline						21						
		B) inulin	C	45 d						26						
		C) sodium butyrate + inulin		Baseline						29						
		D) placebo	D	45 d						32						
		Breakfast test meal		45 d						22						
		T2DM (BMI:: 33.3 kg/m <sup>2</sup> )								21						
Müller et al. 2020 [81] <i>n</i> = 48 RPCT	RIA <sup>1</sup>	12 wks	IG	Baseline	24		32		31	31	31	29	30	8	90 min: 1767	↓ early AUC (0-90 min) in IG compared with CG
		IG: Prebiotics (15 g/ d Arabinosylan- Oligosaccharide)		12 wks	23		24		26	31	30	25	90	8	90 min: 1487	
		CG: Placebo	CG	Baseline	23		31		32	30	31	28	60	9	90 min: 1729	
		Breakfast test meal: 2 slices of white bread, fried egg, chocolate milk (412 kcal, 52% CH, 27% F, 19% P)		12 wks	23		32		29	33	28	26	90	10	90 min: 1754	
		NGT (BMI:: 24.5 kg/m <sup>2</sup> )														
Birkeland et al. 2021 [82] <i>n</i> = 25 RPCT cross-over	RIA <sup>1</sup>	6 wks	IG	Baseline	28		50	47	40	42	39	37	30	22	180 min: 7180 <sup>#</sup>	- ↔ AUC - ↓ decrease in postprandial
		IG: Prebiotics (16 g/ d inulin-type fructans) CG:		6 wks	27		44	45	40	40	36	36	45	18	180 min: 6979 <sup>#</sup>	
			CG	Baseline	27		47	47	40	41	37	36	30 45	20	180 min: 6998 <sup>#</sup>	
				6 wks	28		58	54	45	45	39	36	30	30	180 min: 7596 <sup>#</sup>	

(continued on next page)

TABLE 6 (continued)

Author, (y), n	GLP-1 assay	Intervention Participant characteristics	GLP-1 values (pmol/L) at time points (min)								TTP (min)	Δ Peak (pmol/L)	GLP-1 AUC (pmol/L *min)	Results
			0	20	30	45	60	90	120	180				
excursion in IG compared with CG														
Placebo														
Mixed meal test														
(Fresubin Drink														
vanilla + Jucy														
Drink apple, 550														
kcal, 78.5 g CH,														
15.6 g F, 24 g P)														
T2DM (BMI: 29.1														
kg/m <sup>2</sup> )														

GLP-1 concentrations for selected time points of blood sampling, time-to-peak as well as peak (peak concentration – fasting concentration), and —if available—AUC values are listed. Under “results” only significant results are listed. Time point 0 describes fasting concentrations, and time points >0 are reporting postprandial concentrations. Under “results” only significant results are listed. #original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups, ↔ no differences of GLP-1 secretion between groups. [Supplemental Table 6](#) shows GLP-1 values for all measured time points. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:

**Abbreviations:** AUC, area under the curve; CH, carbohydrates; CG, control group; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; F, fat; GLP-1, glucagon-like peptide 1; iAUC, incremental area under the curve; IG, intervention group; LOD, limit of detection; min, minutes; n.a., not available; NGT, normal glucose tolerance; NW, normal weight; P, protein; RIA, radioimmunoassay; RPCT, randomized placebo-controlled trial; TTP, time-to-peak; T2DM, type 2 diabetes mellitus.

<sup>1</sup> RIA [standardized assay (41)], polyclonal antiserum no. 89390, LOD: 1 pM, intra-assay CV: 6%, specificity: 100% for GLP-1 (7–36) 89% for GLP-1 (9–36);

<sup>2</sup> ELISA (ZellBio GmbH, Berlin, Germany), sensitivity: 8.2 pg/mL.

[81]. Recently, Birkeland et al. [82] also found no effects of a 6-wk prebiotic treatment with 16 g/d inulin-type fructans on the GLP-1 response to a mixed meal test (300 mL of 2 nutritional drinks containing 550 kcal, 78.5 g carbohydrates, 15.6 g fat, and 24 g protein) in participants with T2DM. Roshanravan et al. [23] conducted a double-blind RCT on the effects of prebiotic butyrate and inulin supplementation over 45 d on food-stimulated GLP-1 concentrations in 60 patients with T2DM. The participants were randomly assigned into 1 of 4 groups: Group A received sodium butyrate capsules, group B received inulin supplement powder, group C was exposed to the concomitant use of inulin and sodium butyrate, and group D received a placebo for 45 consecutive days. Butyrate (group A) and butyrate combined with inulin (group C) supplementation led to significant increases in postprandial GLP-1 concentrations 120 min after non-standardized breakfast when compared with the placebo group. Intra-group comparisons between baseline and after 45 d showed a trend for higher GLP-1 values after butyrate, inulin, and butyrate + inulin supplementation. Within all groups, there were no significant changes in body weight in any of the groups after 45 d [23].

In a triple-blind RCT, Rabiei et al. [83] investigated the effects of synbiotic (a combination of a probiotic and a prebiotic) supplementation accompanied by a weight-loss diet in 46 adults with metabolic syndrome over 12 wks. All participants followed a weight-loss diet and were randomly assigned to receive either a synbiotic supplement (consisting of 7 probiotic strains (2×10<sup>8</sup> CFU for all strains) plus 125 mg fructooligosaccharides as prebiotics) or a placebo. Although the fasting GLP-1 concentrations increased in both groups, the increase in the synbiotic group was significantly greater than that in the placebo group [83].

After reviewing these 6 human intervention studies with different methodological approaches, the data regarding the effect of prebiotic, probiotic, and synbiotic interventions on GLP-1 secretion appear inconclusive. It is important to mention that in all 6 studies, the drop-out rate was low (<15%).

Discussion

We analyzed several studies investigating fasting-, glucose-, or food-stimulated GLP-1 secretion under different metabolic conditions. Both fasting and postprandial concentrations of GLP-1, including AUC/iAUC values, the time, and delta-to-peak concentrations, were extracted and evaluated in detail, allowing us to map the physiologic course of the GLP-1 response in numerous studies. Based on the large number of studies analyzed, it is possible to assess the relationship between GLP-1 secretion and metabolic factors, as well as to estimate the impact of dietary interventions on GLP-1 secretion.

Although some studies showed decreased GLP-1 secretion in patients with IGT and T2DM after both OGTT [39,45,46,48] and MMTT or challenge meals [44,56], others reported an increased [42,44,50,55] or unchanged [47,49,58,69] GLP-1 response in the IGT and T2DM groups after OGTT or MMTT/challenge meals. The conflicting nature of the results is also evident from studies reporting increased fasting but decreased meal- or glucose-related GLP-1 concentrations in T2DM [38] and nonspecified diabetes [51], or unchanged fasting but reduced early postprandial GLP-1 concentrations in participants with low insulin sensitivity than in those with high insulin sensitivity [57]. Here, it is important to mention that studies that also include NW/NGT individuals [47,50] can provide a more comprehensive picture of GLP-1 secretion, and possible step-wise alterations, across different metabolic stages than the studies that only compare OW and T2DM [53].



**TABLE 7**  
Fasting GLP-1 values before and after pro- and synbiotic interventions

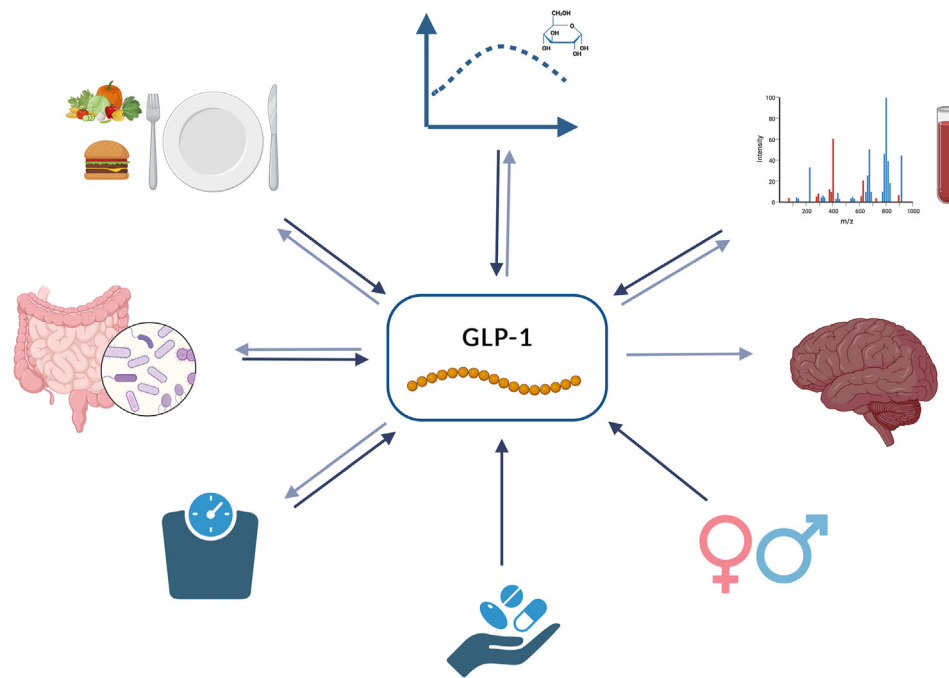
Author, (y), n	GLP-1 assay	Intervention Participant characteristics	Fasting GLP-1 values		Δ	Results
			Baseline	Endline		
Rabiei et al. 2018 [83] n = 46 RPCT	ELISA <sup>1</sup>	3 mo IG: Synbiotics CG: Placebo + energy-restricted diet (-500 kcal/day) MetS (BMI: 32.3 kg/m <sup>2</sup> )	IG 8.1 (ng/mL) <sup>#</sup>	10.2 (ng/mL) <sup>#</sup>	2.1	↑ fasting values compared with baseline and CG
			CG 5.9 (ng/mL) <sup>#</sup>	6.3 (ng/mL) <sup>#</sup>	0.4	
Rondanelli et al. 2021 [80] n = 25 RPCT	ELISA (Invitrogen, ThermoFischer Sci) <sup>2</sup>	60 d IG: Probiotics CG: Placebo + energy-restricted diet (-800 kcal/d) OW (BMI: 34.8 kg/m <sup>2</sup> )	IG 10.9 (pmol/l) <sup>#</sup>	8.6 (pmol/l) <sup>#</sup>	-2.3	↓ fasting values in IG and CG compared with baseline
			CG 7.3 (pmol/l) <sup>#</sup>	5.3 (pmol/l) <sup>#</sup>	-2	

Fasting GLP-1 concentrations as well as Δ (endline value – baseline value) before and after pro- or synbiotic intervention are listed. Under “results” only significant results are listed.  
# original data, ↑ higher GLP-1 secretion in comparison to referred groups, ↓ lower GLP-1 secretion in comparison to referred groups. Details on GLP-1 assays as stated in the publications or according to manufacturer instructions:  
*Abbreviations:* CG, control group; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; GLP-1, glucagon-like peptide 1; IG, intervention group; MetS, metabolic syndrome; OW, overweight; RPCT, randomized placebo-controlled trial.  
<sup>1</sup> n.a.;  
<sup>2</sup> intra- and inter-assay CV: 3.6%.

When comparing fasting GLP-1 concentrations between groups with different metabolic conditions, or before and after dietary intervention, it is important to note that fasting levels are often close to the detection limits of the respective assays and are not well characterized. Only clear changes in fasting levels may be related to metabolic alterations; the mechanisms underlying these changes remain unknown. Therefore, it is important to evaluate critically whether statistically significant changes have any metabolic consequences. It cannot be excluded that an increase in the fasting state is associated with metabolic effects, although this has not been experimentally established. Population-based studies have reported that elevated fasting total GLP-1 concentrations are predictive of increased liver fat [84] and cardiometabolic risks [85], whereas higher physical activity is associated with lower fasting GLP-1 concentrations. The underlying mechanisms still need to be elucidated because it is not clear whether elevated fasting GLP-1 values precede the increase in insulin and subsequent glucometabolic changes (including weight gain) [85] or vice versa. Enhancing GLP-1 activity and targeting GLP-1R activation are key areas of interest for the management of OW and T2DM. High postprandial GLP-1 secretion is beneficial for insulin-dependent glucose control and appetite inhibition and satiety, facilitating its use for the prevention and treatment of OW [86,87]. Although diet-induced enhancement of GLP-1 secretion seems to hold potential, it is important to emphasize that it does not represent an alternative to pharmacologic treatments for T2DM, but rather a preventative or supplementary approach. As shown in a recent meta-analysis, GLP-1R agonist-based treatments have convincing effects on glucometabolic outcomes in T2DM [88]. The new promising drug retatrutide, a synthetic triagonist targeting receptors for GLP-1, GIP, and glucagon, showed comparable effects in a phase 2 trial in which different dosages were administered along with diet and exercise treatment [89]. The American Diabetes Association and the European Association for the Study of Diabetes also highlight the importance of body weight management through diet and physical exercise which play an integral role in a holistic approach to T2DM management [90]. In some of the dietary intervention studies, effects on glucometabolic outcomes were measured in addition to the impact on GLP-1 concentrations, and in some cases, comparable effects have been shown [72,74,77]. However, comparing diet-induced effects to those of pharmacologic treatments has limitations, as the study designs are heterogeneous.

These conflicting results indicate that the relationship between altered GLP-1 secretion and OW and IGT, and more importantly, the direction of this association cannot be conclusively established. This may, in part, be due to various influencing factors, such as the metabolic profile, sex, gut microbiome, diet, glucose tolerance, medication, and BMI (Figure 2). Moreover, when interpreting the GLP-1 values from the studies, the variability in the methods of GLP-1 measurement needs to be considered because different assays differ in their sensitivity, specificity, and coefficients of variation, which could lead to divergent results [91, 92]. However, although absolute GLP-1 values may vary among different assays, the pattern of postprandial secretion appears to be similar [92]. Yet, most reported studies used a standardized assay based on RIA methodology [41]. Studies measuring active GLP-1 were not included because active GLP-1 is low in abundance, which can lead to high variability and low accuracy [31]. In addition, the time taken to reach peak GLP-1 concentration is only comparable to a limited extent, as blood collection was performed at different time points and, so far, no continuous GLP-1 measurement is possible.





**FIGURE 2.** Main influencing factors of GLP-1 secretion. GLP-1 secretion may be modulated by several factors, such as the gut microbiome, eating behavior, glucose tolerance, metabolic profile, sex, medication, and body mass index (indicated by dark blue arrows). GLP-1 also affects these factors (except sex and medication), in addition to its neuroprotective properties (indicated by light blue arrows). GLP-1, glucagon-like peptide 1.

### Impact of BMI

BMI is an important factor influencing GLP-1 secretion, even after correcting for metabolic differences, with GLP-1 responses decreasing with increasing BMI [38, 45]. The bivariate analysis of the study population stratified by OW convincingly showed an independent contribution of BMI on insulin release,  $\beta$ -cell glucose sensitivity, and GLP-1 response, whereas GLP-1 responses were gradually depressed across increasing degrees of OW [45]. Interestingly, when receiving an equivalent dose of a GLP-1 analog, individuals who were OW exhibited metabolic and appetite responses similar to those of their healthy matched controls [93], suggesting that sensitivity to GLP-1 is maintained in OW. Because OW and T2DM often occur simultaneously, separating the impact of elevated body weight from impaired glucose control is challenging. As BMI in the OW study groups ranged between 29 kg/m<sup>2</sup> [53] and 39 kg/m<sup>2</sup> [74], the grade of OW within the study cohorts could have contributed to the contradictory results of this review.

In addition to BMI, weight loss may also influence the GLP-1 response. Studies have reported that the meal response of GLP-1 increases after weight loss [72,94,95] and even during weight maintenance [72]. Regarding fasting GLP-1 concentrations, data are more inconsistent because some studies showed unchanged levels during acute and maintained weight loss [74,95], whereas others reported decreased values [79,80]. In addition, although in some studies higher fasting GLP-1 concentrations were observed after an energy-restricted diet, it is important to note that these occurred only in the intervention groups combining a calorie restriction with an additional intervention such as synbiotic supplement [83], MIND diet [73] or healthy nordic diet [72], whereas there was no effect in the control groups. These results indicate that weight loss during hypoenergetic intervention studies [72–74,79] may also influence GLP-1 secretion when

compared with isoenergetic dietary approaches [76]. However, the effects of the specific diets or alternative interventions seem to be important, and additional differences in study designs, such as intervention duration, extent of calorie reduction, and participant characteristics, need to be considered.

### Impact of glucose tolerance

The effect of GLP-1 on glucose tolerance has been the focus of numerous studies. The observation that GLP-1 responses may be blunted in T2DM [29,38,96,97] has led to the notion that an impaired incretin effect contributes to the  $\beta$ -cell incompetence found in diabetes [29]. Clinical data showing that GLP-1 analogs can normalize glycemia by stimulating insulin secretion in T2DM strengthen the incretin hypothesis [98,99]. Besides, in a few studies, impaired GLP-1 secretion and impaired GIP secretion have been found in individuals with IGT or T2DM [38]. The incretin effect of GLP-1 and GIP has been demonstrated in animal studies, and now, with the help of antagonists for both receptors, the importance of incretin hormones for the maintenance of NGT has been demonstrated [31,100–102]. Therefore, impaired incretin secretion may contribute to the development and clinical worsening of diabetes mellitus.

The meal-stimulated GLP-1 response of individuals with IGT ranged between healthy participants and patients with T2DM, independent of sex and BMI [38]. This suggests that GLP-1 response correlates strongly with glucose tolerance. At the same time, an unexpected positive correlation between fasting blood glucose concentrations and GLP-1 secretion in T2DM has been described, which led to the hypothesis that hyperglycemia is unlikely to be responsible for the impaired GLP-1 response in T2DM. However, in multiple regression analyses, diabetes was found to be a decisive determinant of GLP-1 secretion [38]. These results are consistent with the findings in monozygotic twins discordant

for T2DM, where the new dimension of the “incretin defect” was added to the complicated and self-perpetuating process involved in the development of noninsulin-dependent diabetes [96]. Moreover, the incretin effect on total insulin secretion and  $\beta$ -cell glucose sensitivity, when investigated separately, and the GLP-1 response to oral glucose were reduced in T2DM compared with NGT or IGT. Further, the GLP-1 response was inversely related to glucose tolerance (plasma glucose concentrations after 2 h) [45]. In twin pairs discordant and concordant for OW, an acquired unhealthy pattern of OW, characterized by liver fat accumulation and insulin resistance, was closely related to an impaired glucose-stimulated GLP-1 response [103]. An additional explanation for the difference in GLP-1 secretion between healthy individuals and patients with T2DM is that the number of incretin-expressing enteroendocrine cells in the jejunum containing both GIP and GLP-1 [104, 105] were increased in the diabetic state in some studies [42]. Therefore, the reciprocal influence of GLP-1 secretion and glucose homeostasis is of great interest when evaluating glucose- and food-dependent GLP-1 responses. Additionally, the BMI of the T2DM study groups varied between 23.5 kg/m<sup>2</sup> [47] and 38.5 kg/m<sup>2</sup> [48], which led to a heterogeneous group of participants across the studies despite having the same co-morbidity.

An increasing body of clinical evidence suggests that antidiabetic agents directly affect GLP-1 secretion. Metformin treatment increases fasting and postprandial GLP-1 concentrations, both over the short-term [106–108] and over the mid-term to long-term [109–112] and in patients with [106,109,112] and without T2DM [107,108,110–112]. In human gut cells, metformin is a direct secretagogue for GLP-1 release from L cells [106]. In addition, bile acid sequestrants may increase fasting- and meal-stimulated GLP-1 secretion in patients with T2DM [113]. Furthermore, an altered gastric emptying rate after short and long-term metformin administration in T2DM has been reported [114, 115]. Although the results were contrary, these studies highlight the potential influence of metformin therapy on gastric emptying and GLP-1 secretion [116]. In addition, other antidiabetic agents, such as GLP-1 receptor agonists or DPP-IV inhibitors, delay gastric emptying in individuals who have OW [117, 118] or T2DM [119]. However, some studies have reported no change in gastric emptying [120,121]. Therefore, it is important to consider the impact of prevailing diabetes control when investigating GLP-1 secretion in patients with and without diabetes, especially when antidiabetic agents are administered on the day the meal tests are conducted. Different inclusion and exclusion criteria of the studies and different approaches on the examination days could have resulted in the observed discrepancy in results in participants with and without T2DM—although some studies in this review excluded patients receiving antidiabetic therapy [47,64, 71,76], others included them [65,79]. Furthermore, study populations with the same BMI but different stages of glucose tolerance are highly useful to investigate the influence of glucose tolerance independent of BMI [46,53], in contrast to study groups where BMI and glucose tolerance vary simultaneously.

In summary, the current evidence emphasizes the importance of a detailed assessment of glucose metabolism and diabetes control in study participants when examining GLP-1 secretion. A recent study also showed that the increase in GLP-1 concentrations after ingestion of a glucose solution compared with a sucrose solution depended on the insulin sensitivity of the participants [122]. This emphasizes that the degree of glucose tolerance, separately and in combination with the nutrient composition and type of carbohydrates, influences carbohydrate-stimulated GLP-1 secretion. The relationship between

impaired incretin secretion and impaired glucose tolerance is of great scientific interest and certainly a key element in further studies.

### Impact of meal composition or size

As described above, several studies have suggested that meal composition and size are important factors influencing the postprandial GLP-1 response. Although it is reasonable to assume that macronutrients and their digestive products specifically stimulate GLP-1 secretion, we have only begun to understand the underlying mechanisms in humans, and the possible mechanisms of nutrient-stimulated GLP-1 secretion from various experiments have recently been reviewed elsewhere [123].

Glucose, protein, and fat have been described to be strong GLP-1 secretagogues after they have been orally ingested or directly administered into the intestine [32,124–126]; with carbohydrate and proteins eliciting earlier peaks in GLP-1 secretion (30–60 min postprandially) than lipids (>120 min postprandially) [32,127]. However, the role of macronutrient composition in GLP-1 secretion in OW or IGT, or T2DM has not been fully elucidated. Some evidence points to a major influence of carbohydrate concentrations (including fiber), wherein a carbohydrate-rich test led to higher postprandial GLP-1 secretion than test meals containing less carbohydrates in T2DM [65,69]. Already in 1955, it was demonstrated that sucrose stimulates GLP-1 secretion through both early and late mechanisms involving luminal contact [128]. Apart from the amount of carbohydrates, the type of simple carbohydrate appears to play an important role in GLP-1 secretion. A study in healthy individuals with OW showed that ingestion of a 75-g sucrose load provoked a less robust postprandial rise in GLP-1 concentration compared with an equicaloric 75-g glucose load [122]. Similarly, test drinks with a modified carbohydrate composition [regular alcohol-free beer, alcohol-free beer with the fermentation of the regular carbohydrates and enriched with resistant maltodextrin (and isomaltulose)] led to a higher GLP-1 response than the regular test drink (containing glucose) [59]. Some study results illustrate the confusion in this field, as a reduced amount of carbohydrates, as a possible explanation for reduced GLP-1 concentrations, contrasts with the higher fiber content of the Okinawan-based Nordic Diet, examined by Ohlsson et al. [79].

In addition, for protein and amino acids, stimulation of GLP-1 secretion by a higher content than control meals has long been demonstrated in vitro and in vivo in the short and long-term and in both NW or OW groups and healthy individuals, and with T2DM [68,74,78, 129–132]. Although the interaction of proteins with intestinal endocrine cells is still under investigation, amino acids (the breakdown products) have been more thoroughly studied. The amino acid composition of proteins seems to be relevant as amino acids differ in their GLP-1 stimulatory potential [133], which may partly explain the heterogeneous study results. Some amino acids appear to stimulate L cell secretion from the luminal side, whereas others may interact basolaterally with receptors following absorption [133,134]. Moreover, protein hydrolysates stimulated ileal GLP-1 secretion in male rats [135].

Even if the cell density of intestinal GLP-1-releasing L cells, which are expressed in the entire small intestine and colon, is highest in the ileum and colon, a considerable number of L cells are also found in the duodenum and proximal jejunum, thus leaving the possibility of a common mechanism for carbohydrates, proteins, and fat involving intestinal L cells releasing GLP-1 as a response to direct nutrient contact [42,136,137]. Experimental studies have shown that the

proximal part of the gut is responsible for most early GLP-1 responses to meal ingestion [135]. Multiple studies showing a gastric emptying time of <1 h [138] underline the possibility that nutrients, especially after a fast transit of liquid meals or glucose solutions, can reach the duodenum in a short time, leading to GLP-1 release from L cells. This could explain the observed peaks in GLP-1 concentrations, even in short-term postprandial protocols with a duration of ~3 h. As summarized in the same review, the shortest small intestine transit time reported was 3.3 h, leaving a short time for the luminal content to come in contact with L cells located in the jejunum or even the ileum and stimulate the chemo-sensing machinery, leading to the modulation of GLP-1 release. Moreover, according to the results of a very early study, the presence of appropriate nutrients in the upper small intestine could induce very early postprandial GLP-1 release (~15 min after meal ingestion) via an indirect pathway, possibly involving enteroendocrine nerves. Furthermore, sparse GLP-1-producing cells present in the upper intestinal tract may be sufficient to produce the increment observed in the early postprandial phase [128]. The colonic contribution to postprandial L cell secretion is unknown, and secretion from the colon is probably not normally related to nutritional stimulation but rather to malabsorbed bile acids and microbial metabolites [139].

The sweet taste receptor expressed by human duodenal L cells, which binds to sugars, sweeteners, sweet amino acids, and sweet proteins has been suggested to be involved in GLP-1 secretion [140, 141]. In rodents, it has been shown that taste cells also express GLP-1, which may enter the circulation [142]. Even if the concentration of GLP-1 released from taste cells is limited, because of the near absence of DPP-IV compared with GLP-1 released from L cells in the distal intestine, it may exert a larger effect than expected [143]. As it seems possible that glucose may reach the duodenum during the 3-h test of an OGTT, it might be speculated that sweet taste receptors may be involved in postprandial GLP-1 elevations during OGTTs. However, further studies are warranted to elucidate the function of taste receptors in glucose-stimulated GLP-1 secretion *in vivo*.

As it is undisputable that liquids empty from the stomach more quickly than solid meals, the physical state of the test meal applied in the reviewed studies had a decisive effect on L cell-mediated GLP-1 secretion [138]. In addition, the size of the meal seemed to matter; the late GLP-1 response (30–180 min) to a large meal (520 kcal) was shown to be more pronounced than that to a small meal (260 kcal), possibly due to lower exposure of stimulatory nutrients to the L cells following the small meal [56]. The secretory capacity of the distal small intestine is thought to be related to the role of GLP-1 as an “ileal brake” hormone, which is part of an inhibitory feedback mechanism that signals nutrient abundance to the brain, promotes satiety, and inhibits upper gastrointestinal motility and secretion [139,144,145]. Therefore, the distal part of the small intestine appears to be more involved in responses to larger meals as well as in connection with changes in intestinal transit times [146]. However, other studies reported that the quantity of a meal is less influential than its composition [69]. The effects of meal size on GLP-1 secretion have been reviewed and discussed in more detail elsewhere [147–149].

As carbohydrates, fats, and proteins have different cephalic phase responses and effects on gastric emptying when ingested in isolation [150], it is important to consider gastric emptying and transit time when analyzing the impact of meal composition on GLP-1 secretion. It is also long known that GLP-1 secretion is directly influenced by the rate of gastric emptying. This indicates that food selection is particularly important for GLP-1 secretion in patients with (pre)diabetes. Although the inhibitory effect of GLP-1 on appetite and satiety is well

documented, first proposals suggest that alterations in gut hormone secretion could also lead to changes in macronutrient-specific food preferences, favoring lower-calorie foods [151]. This is supported by the observation that elevated fasting and postprandial GLP-1 secretion after bariatric surgery are associated with the magnitude of weight loss [152, 153]. Elevated nutrient delivery to the distal small intestine is likely the predominant mechanism behind the exaggerated GLP-1 response after gastric bypass [123,154]. Although complex physiologic changes occur after bariatric surgery, which is not the topic of this review, this highlights the idea that diets could be designed to enhance L cell sensing and satiety through nutrients that stimulate GLP-1 and other gut hormones.

Moreover, other dietary factors, such as secondary plant compounds, can influence postprandial GLP-1 secretion, for example, by counteracting oxidative stress and the associated upregulation of DPP-IV activity [61,155,156]. In addition, it is speculated that the degree of food processing influences GLP-1 secretion and glucose metabolism, for example, via the impact of altered starch properties or food additives including antimicrobial preservatives and monosodium glutamate in ultra-processed foods [157–160]. Food processing also affects digestibility, tolerance, and nutrient accessibility [161]. Considering the content of secondary plant compounds and the grade of processing of the test meals applied in the studies reviewed could explain the contrary results, especially when applying westernized test diets containing processed foods [38,44,49,56–58,60,65] or test diets with a high percentage of fruits and vegetables [63,65,68,72,73,79].

### Impact of sex

In some studies, sex was a significant determinant of GLP-1 secretion. Male participants had ≤20% smaller postprandial GLP-1 response to the test meals than females [38,49,96,122]. Interestingly, in one study, this effect was observed in individuals with NGT, but not in those with IGT or T2DM [39]. Supporting an enhancing effect of estrogens on incretin responses, estradiol was described to positively regulate oral glucose-induced GLP-1 response in mouse and human  $\alpha$ - and L cells [162]. In addition, an impact of the menstrual cycle was reported to influence GLP-1 secretion in women. It was shown that gastric emptying of glucose was slower and GLP-1 concentrations were lower during the follicular compared with the luteal phase [163]. Therefore, the sex distribution and lack of consideration of the menstrual cycle phase for female participants within the study cohort could also have influenced the study results. A few studies discussed in this review including only women [72,73] or men [57] allow a sex-independent evaluation of GLP-1 secretion, whereas this is not possible in studies including both sexes.

### Impact of the gut microbiota

Alterations in the gut microbiota (dysbiosis) may be associated with the pathogenesis of metabolic diseases [164–167]. Recent studies have demonstrated the impact of the gut microbiota on the therapeutic effect of metformin in patients with diabetes [168]. Although causal relationships have been well demonstrated in animal models, studies investigating the underlying functional pathways in humans are required [166,169]. GLP-1 has various physiologic actions, including anorectic and neuroprotective effects, and has been suggested to play a central role in the microbiota-gut-brain axis and disease pathogenesis [9,170–172]. One link between GLP-1 and the gut microbiota may be microbial metabolites, such as SCFAs from bacterial fermentation of fiber, which may stimulate GLP-1 secretion via FFAR2 and FFAR3;

however, as discussed above, this may not apply to humans. Moreover, as the effect of bacterial metabolites would presumably be time delayed, it is likely that they affect fasting GLP-1 concentrations or secretion in the long run and might not be observed in postprandial protocols of 3-h duration [173]. This makes gut microbiota a potential target for dietary and pharmaceutical interventions aimed at modulating basal GLP-1 secretion, thereby preventing or treating T2DM and other metabolic disorders. Conversely, GLP-1 receptor agonists may affect the gut microbiome composition in mice and in patients with T2DM consuming liraglutide. The underlying mechanisms are yet to be elucidated in detail but modifications of gastric emptying, along with changes in caloric intake, and modifications in gut pH levels and nutrient availability are being evaluated [174].

Altogether, the results from the mid- to long-term human trials presented in this review support the outlined relevance of the interaction between diet and gut microbiota for GLP-1 secretion. Moreover, they indicated that a longer intervention duration might be necessary to achieve the desired effects on GLP-1 concentrations. It also became obvious that, in addition to uncontrolled studies [79] or studies with a control group that also experienced an alteration of the habitual dietary behavior, e.g., through an energy restriction [72–74], long-term dietary interventions with a control group that does not change its habitual diet are highly needed. Three studies directly targeting the gut microbiota with synbiotic, prebiotic, and probiotic supplements showed significant positive effects on GLP-1 concentrations and other metabolic parameters (e.g., synbiotic's effect on insulin resistance, probiotic's effect on insulin secretion, and prebiotic's (inulin and butyrate) effect on fasting glucose [23,43,83]). Unfortunately, only Simon et al. [43] directly examined the effects of the intervention on gut microbiota composition and found differences in the supplemented bacterial strain *L. reuteri* (whereas there were no differences in other bacteria). When interpreting the results of these studies, it is important to consider the differences in methodologies. Probiotic, prebiotic, and synbiotic interventions are fundamentally different approaches, and the reported studies vary in the bacterial strains and prebiotic substances implemented, duration and type of the intervention (e.g., additional energy-restricted diets), and variations in using several types of GLP-1 assays. These are the general limitations of clinical probiotic-, prebiotic-, and synbiotic intervention studies leading to heterogeneous and sometimes inconclusive results that need to be addressed in microbiome research [175]. Furthermore, the difference in drop-out rates of <20% [23,43,81,82] compared with >20% [72,74,79] could have had a decisive impact on the results.

### Future research needs

The heterogeneity of the subject groups affected the comparability of the cohorts; for instance, not all studies considered the medication of patients with T2DM, even though it has been previously reported that antidiabetic agents directly affect fasting and postprandial GLP-1 secretion and gastric emptying. There was also high variation in the average BMI and range of the study populations. For example, in the NGT groups, the BMI of the participants varied between 21.3 kg/m<sup>2</sup> and 35.5 kg/m<sup>2</sup>, and not all studies had subgrouped participants into lean and having OW. As outlined above, an association between BMI and GLP-1 secretion has been shown in several studies, which probably contributes to conflicting results. Moreover, not all studies evaluated the degree of glucose (in)tolerance in the study population. Therefore, for future studies, it is highly relevant to thoroughly characterize their cohorts according to BMI, sex, ethnicity, age,

glucose tolerance, medication, and health status, as well as assess habitual diet and physical activity to improve the comparability of the cohorts.

Regarding the assessment of the impact of meal composition or size on GLP-1 secretion, applying standardized methods for the MMTT and challenge meals would help improve comparability between studies. As for example, the amino acid composition of proteins can affect GLP-1 secretion, future studies need to analyze the composition of the meal tests applied in detail. In addition, it is essential to assess gastric emptying rate and transit time to fully understand the impact of certain test meals on GLP-1 secretion.

Additionally, further mid- to long-term studies should be conducted to investigate the modulation of GLP-1 secretion by dietary pattern interventions or prebiotic, probiotic, and synbiotic interventions after accounting for factors such as glucose tolerance, other metabolic and gut-brain axis-related parameters, and gut microbiota, to generate a more comprehensive understanding of the complex interrelations and consolidate knowledge about the underlying mechanisms.

In summary, the application of highly standardized meal tests with detailed analyses of nutrient composition and gut-related outcomes, especially gastric emptying, in well-defined cohorts is crucial to derive robust conclusions.

### Conclusion

This review has demonstrated that studies on fasting GLP-1 concentrations and glucose- and food-stimulated GLP-1 responses in individuals with different metabolic conditions are inconsistent, but there is convincing evidence that these responses may be influenced by the metabolic profile, sex, gut microbiome, glucose tolerance, BMI, anti-diabetic medication, eating behavior, and nutrient composition.

Some studies have indicated that GLP-1 secretion is impaired in patients with IGT or T2DM, and consistently more so in individuals who have OW. Considering the relevance of GLP-1 in glucose homeostasis, eating behavior, weight maintenance, and neuroprotection, these results are important for both healthy individuals and patients with metabolic impairments.

In addition, this review highlights that GLP-1 secretion can be modified exogenously through dietary interventions. As more attention is being drawn to dietary habits or food patterns, it has become evident that a holistic approach and studies on the influence of long-term diets on health and GLP-1 release are more important than examining single nutrients or foods. To date, only a few studies have focused on the effects of food patterns on GLP-1 secretion and thus on metabolism, the immune system, and the microbiota-gut-brain axis [79,176,177]. These findings indicate that food selection is particularly important for GLP-1 secretion in patients with diabetes, and has great potential for the prevention and holistic treatment of IGT, T2DM, and OW. However, further nutritional intervention studies are needed to examine over mid- and long-term.

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### Author contributions

The authors' responsibilities were as follows – HH, AS: conducted the research and prepared the first draft of the manuscript, which was



subsequently finalized in close collaboration with MCS and JJH; all authors: provided substantial content contributions and edited the manuscript; MCS: had the initial idea for this manuscript; AS, MCS: created and edited the figures; and all authors: have read and approved the final version of the manuscript.

### Conflict of interest statement

The authors report no conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajcnut.2024.01.007>.

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