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Artículo de Revisión Sistemática / Systematic Review Article

Effect of chewing behavior modification on food intake, appetite and satiety-related hormones: A Systematic Review

Efecto de la modificación del comportamiento masticatorio sobre la ingesta de alimentos, apetito y hormonas relacionadas con la saciedad: Una Revisión Sistemática

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ABSTRACT

Purpose: Obesity has become a growing public health issue worldwide. Studies have shown that eating rate is one of the most important factors to consider in the strategies to prevent and/or treat obesity. Eating rate can be reduced through different strategies, such as an increase in oro-sensory exposure, the modification of food texture, and an increase in the number of chewing cycles. The aim of this systematic review was to analyze the available evidence regarding the effect of chewing behavior modification on the parameters that contribute to obesity. Methods: A systematic search was done on the electronic databases Pubmed, Cochrane Central Register of Controlled Trials, and Scopus, using the terms "mastication", "chewing", "chewing speed", "prolonged chewing", "number of chews", "masticatory cycles" "satiety" "satiety response" "appetite", "appetite regulation", "nutritional status" and "obesity". Results: A total of 23 intervention studies were selected that intervened in the participants' chewing behavior, either by reducing the eating rate, increasing oro-sensory exposure, food hardness or the number of chewing cycles. In most studies these interventions were effective at reducing food intake, subjective appetite and improving the plasma levels of satiety-related hormones and metabolites; moreover, they reduced body mass index in the long term. Conclusion: The currently available evidence seems to indicate that modifications to chewing behavior can bring with it a myriad of benefits for the treatment of obesity.
Keywords: Appetite; Chewing behavior; Eating rate; Food intake; Gastrointestinal hormones; Obesity; Satiety.

RESUMEN

Propósito: La obesidad se ha convertido en un problema de salud pública creciente a nivel mundial. Investigaciones han demostrado que la tasa de ingesta es uno de los factores importantes a considerar en las estrategias para prevenir o tratar la obesidad. La tasa de ingesta puede reducirse a través de diferentes estrategias; el aumento de la exposición oro-sensorial, la modificación de la textura de los alimentos y el aumento en el número de ciclos masticatorios. El objetivo de esta revisión sistemática fue analizar la evidencia disponible sobre el efecto de la modificación de la conducta masticatoria sobre los parámetros que contribuyen a la obesidad. Métodos: Se realizó una búsqueda sistemática en las bases de datos electrónicas Pubmed, Cochrane Central Register of Controlled Trials y Scopus, con los términos "mastication", "chewing", "chewing speed", "prolonged chewing", "number of chews", "masticatory cycles" "satiety" "satiety response" "appetite", "appetite regulation", "nutritional status" y "obesity". Resultados: Se seleccionaron 23 estudios que intervenían en el comportamiento masticatorio de los participantes, ya sea reduciendo de la tasa de ingesta, aumentando la exposición oro-sensorial, dureza de los alimentos y número de ciclos masticatorios. Estas intervenciones resultaron ser efectivas para reducir la ingesta de alimentos, el apetito subjetivo y mejorar los niveles plasmáticos de las hormonas y metabolitos relacionados con la saciedad, además, a largo plazo, permitieron reducciones en el índice de masa corporal. Conclusión: La evidencia disponible actualmente parece señalar que las modificaciones en el comportamiento masticatorio pueden traer consigo múltiples beneficios para el tratamiento de la obesidad.

Palabras clave: Apetito; Comportamiento masticatorio; Hormonas gastrointestinales; Ingesta de alimentos; Obesidad; Saciedad; Tasa de ingesta.

INTRODUCTION

Obesity has become a growing public health issue globally[1], and this significantly increases the risk of morbidity due to chronic diseases such as type 2 diabetes, cardiovascular diseases and certain types of cancer, among others[2]. This is the result of an energy imbalance between calories consumed and energy expenditure, creating an energy surplus and a positive state of energy balance that results in excess body weight. Overweight is associated with a wide variety of risk factors, such as genetic aspects, excessive energy intake and a sedentary lifestyle, among others[2]; thus, current obesity treatments must have an interdisciplinary approach[3]. One of the most important factors to control in obesity treatment is food intake, which is regulated mainly by appetite, satiation and satiety[4,5]. Appetite is defined as the desire to eat, and covers the entire field of ingestion, selection, motivation and preference[6,7]. Satiation refers to the process that leads to the interruption of eating; therefore, it controls intake size, and is also known as "satiety during meals"[7]. Satiety is defined as the reduction in the desire to eat once the meal has finished; it refers to after-meal events that affect the interval until the next meal, thereby regulating meal frequency, and is also known as "satiety between meals"[8,9]. These processes are mediated by a series of physiological, cognitive and sensory mechanisms that together modulate the eating behavior[7].

Previous studies have shown that eating rate (ER) (amount of food ingested/time spent on ingesting the food) is one important factor that contributes to weight gain and obesity, because a rapid ER leads to an alteration in the secretion levels of different satiety-related hormones, an increase in gastric emptying speed and a shorter oro-sensory exposure (OSE) time, among other factors that negatively affect satiety, thus leading to a significant increase in food intake[10,11,12]. It has been shown that ER can be reduced through different strategies, including increased OSE, which induces satiety sooner[13], the modification of food towards a harder texture, which increases oral processing time[14], and the increase in the number of chewing cycles[15], among others. The available evidence has suggested that reducing the ER can have significant effects on the regulation of body weight, which is why it is has been included in the strategies to prevent and/or treat obesity[16].

To date it is known that chewing behavior is closely related to food intake; however, it is necessary to review the evidence based on intervention studies, which assess whether modifying the previously mentioned factors of chewing behavior really has significant effects on the parameters that contribute to weight gain, thus substantiating whether applying such interventions in obesity treatments is justifiable. There are reviews on the subject[17,18]; however, in recent years, new original intervention studies have been published that are not included in them. This review will evaluate the effect of the intervention on chewing behavior in the variations in the amount of food ingested, subjective evaluations of appetite and changes in the plasma levels of satiety-related hormones.

The aim of this systematic review was to analyze the available evidence regarding the effect of chewing behavior modification (such as reduced chewing speed, prolonged chewing, and increased number of masticatory cycles, among others) on the parameters that contribute to obesity (food intake, appetite and levels of satiety-related hormones). It was hypothesized that modifying the previously mentioned factors of chewing behavior has significant effects on some of the parameters that contribute to obesity, thus applying the strategies to prevent and/or treat obesity would be justifiable.

MATERIALS AND METHODS

A systematic review of the literature was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19].

Search strategy. The studies analyzed in this review were identified by searches in the electronic databases Pubmed, Cochrane Central Register of Controlled Trials, and Scopus. The search terms used were "mastication", "chewing", "chewing speed", "prolonged chewing", "number of chews", "masticatory cycles" "satiety" "satiety response" "appetite", "appetite regulation", "nutritional status" and "obesity", which were used in combination by means of the Boolean operators OR and AND. The search was done by two independent researchers in November 2020. To identify possible additional eligible studies not identified by the electronic search, a review was made of the list of references of other pertinent reviews and selected articles.

Eligibility criteria. To be included, articles had to fulfil certain criteria. First, they had to be intervention studies that reported the food ER, the magnitude of OSE, the food texture and/or number of chewing cycles during meals, studies where the participants were classified according to their nutritional state, studies which contained clear information on the methodology of the interventions and adequately reported on the parameters within which the results were evaluated. No limits were set on language or publication date.

The studies where the participants had any type of disease, were under some type of pharmacological treatment, had eating disorders, smoked or reported that the participants worn some type of removable dental prostheses were excluded.

Study selection. The Mendeley software was used to analyze the search results. Two researchers independently assessed the previously described pre-established criteria, and disagreements were resolved by discussion among all the authors. This was done for the review of titles and abstracts as well as for the textual reading of potentially eligible articles. For articles excluded in this final stage, the reason for the exclusion was recorded.

Data extraction. Two reviewers independently extracted the data. The main variables extracted from each study included were: study design, sample size, sex, age and BMI of the participants, test food, follow-up, testing procedure and appetite assessment method.

In relation to the findings of the selected studies, the main extracted variables were the effects of the intervention on the amount of food ingested, appetite, BMI and satiety-related hormones and metabolites.

Risk of bias assessment. The methodological quality of the selected studies was evaluated independently by two reviewers according to the following parameters: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, data on incomplete results and selective reports. Criteria were evaluated as adequate, unclear or inadequate. The studies were considered as having a low risk of bias if two thirds or more of the parameters were considered adequate, and they were considered as having a high risk of bias if less than two thirds of the parameters were considered adequate.

RESULTS

The flow chart that summarizes the selection process appears in figure 1. The electronic search in the three databases yielded a total of 2,000 articles. Eight additional articles were found by manual search. After the removal of duplicates, 1,283 articles were obtained, which were assessed according to their title and abstract, and in total 67 potentially eligible articles were selected, the full texts of which were read. Forty-four articles were excluded, the reasons for which appear in table 1, and 23 articles were selected for the qualitative analysis (references 20 to 42), all corresponding to intervention studies.

Characteristics of the articles included. Most of the studies were conducted in university settings[20,23,24,26,29,30,31,32,33,36,37,39,40,41,42], two were conducted in hospitals[27,35], one with the participants of a physical fitness program[21] and five did not indicate the location[22,25,28,34,38]. The studies were undertaken in the United States[20,21,24,25,34,36,40,4], the

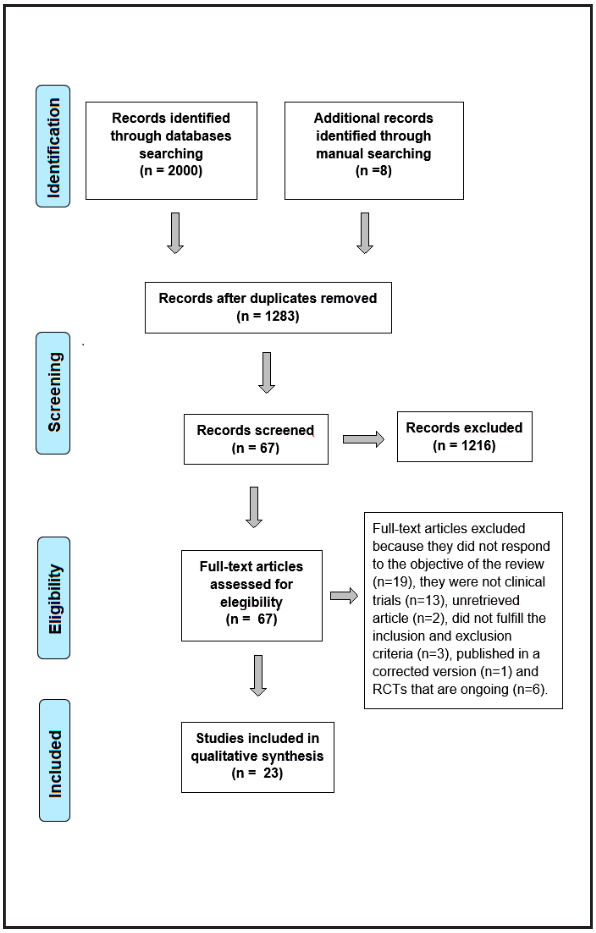

Figure 1: Flow chart of the article selection procedure.

United Kingdom[23,26,27,28,37], the Netherlands[22,31,32,38,42], Australia[35], China[33], Japan[29], France[30] and Sweden[39]. All had the approval of the scientific ethics committee, except one which did not indicate it[21], and one that stated it was not necessary[34].

The summary of the risk of bias of the articles included is described in figure 2. Fifteen studies were considered as having a low risk of bias[20,25,26,29,30,33,34,35,36,37,38,39,40,41,42] and 8 a high risk of bias[21,22,23,24,27,28,31,32].

Characteristics of the participants. The number of participants included in articles varied from 10 to 106 volunteers, and the mean age varied between 20 and 34 years. Most of the studies included men and women, except for four studies that only included male volunteers[30,32,33,40] and four that only included women[20,21,29,39] (Table 2).

Study protocol

Test foods. The test foods varied according to the study, some of them used pizza[21,40,41], pastas[20,21,22,37], sandwiches[23,28], model food gels[31], flan[32], almonds[24], hamburgers[22,29], and others (Table 2).

Testing procedure. The testing procedure varied according to the study, the ER, OSE, food texture, number of chewing cycles and use of oral devices were manipulated (see Table 2).

The chewing behavior was modified from the reduction in the rate of eating, the increase in OSE and the increase in the number of chewing cycles, which is observed in greater detail in Table 2. For this, the studies used different strategies, such as: verbal and/or written instructions[20,21,23,24,28,33,36,37,38,39,40,41], computers[32,34,39], food hardness[22,26,29,30,31,32,42], use of specific equipment such as portable sensors[25] manometer[27] and sensor monitored alimentary restriction therapy (SMART)[35].

Appetite assessment. Most of the studies assessed appetite levels through visual analog scales (VAS)[20,22,23,24,26,28,29,30,31,32,33,34,35,36,37,39,40,41,42]; one study evaluated it through a 10-point categorical scale[21], another one through a 9-point categorical scale[25], one through a 5-point categorical scale[38] and another using the rating scale on a mandometer[27]. Eight of these studies also included a blood analysis in their methodology to observe possible variations in the levels of different metabolites and gastrointestinal and pancreatic hormones related to satiety, such as: plasma glucose, insulin, cholecystokinin(CCK), glucagon-like peptide-1(GLP-1), polypeptide YY(PYY), glucose-dependent insulinotropic peptide(GIP), pancreatic polypeptide(PP) and ghrelin[23,24,27,30,32,33,35,40] (Table 2).

Study outcomes

Effects on intake. The results in relation to food intake in the different conditions varied according to study. 52% of studies[20,22,23,27,31,32,33,34,36,37,39,41] showed that the reduction in the ER, increase in OSE and increase in the number of chewing cycles reduced food intake during the test meals. Some studies analyzed the amount of food ingested in the hours after the test meals, and found that prolonged chewing reduces subsequent food ingestion[26,28], whereas others found no significant differences for the conditions studied[30,40]. This is described in detail in Table 2.

Effects on appetite measurements. The subjective measurements of appetite were analyzed immediately after the test and/or post-prandial meals. The results obtained varied according to the studies and are expressed in detail in Table 2. 43% of studies[21,24,26,29,32,34,35,36,39,40] showed that the reduction in ER, increase in OSE and increase in the number of chewing cycles reduced appetite levels.

Findings in BMI variation. McGee et al.[35] reported

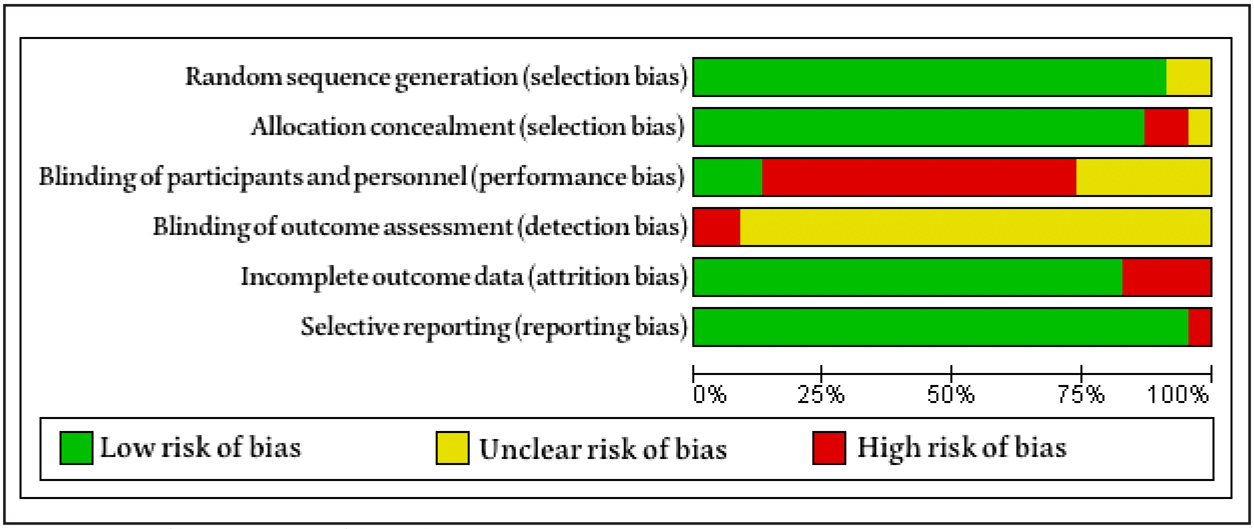

Figure 2: Risk of bias summary of the included studies.

significant variations in BMI from the beginning to the end of the study.

The study by Ford et al. (2009)[27] demonstrated that by the end of the treatment, the experimental group achieved a significant reduction in BMI and in the percentage of body fat.

Findings in the variation of satiety-related hormones. Eight of the selected studies[23,24,27,30,32,33,35,40] included a blood analysis. These showed that chewing behavior modifications, such as; the reduction in the ER, the increase in OSE and the increase in the number of masticatory cycles allowed an increase in insulin levels[32,40]. Carrying out a greater number of masticatory cycles generated an increase in plasma glucose levels[40], GLP-124, CCK and a reduction in ghrelin levels[33,40]. This is described in detail in Table 2.

Table 1. Reasons for exclusion of articles read in full.

Reference	**Exclusion Reasons**
Forde et al., 2013; van den Boer & Mars, 2015; Lasschuijt et al., 2018; Toyama et al., 2015; Krop et al., 2018; Sato et al., 2019; Zijlstra et al., 2009; Hamada et al., 2016; Mattes & Considine, 2013; Spiegel, 2000; Kito et al., 2019; Tan et al., 2016; Westerterp-Plantenga et al., 1990; Spiegel et al., 1993; McArthur et al., 2018; Rugh, 1972; Ruijschop et al., 2011; Hetherington & Boyland, 2007; de Wilk et al., 2008.	Did not respond to the objective of the review.
Stokes et al., 2013; Smeets & Westerterp-Plantenga, 2006; Ioakimidis et al., 2012; Serafim et al., 2014; Hamada et al., 2014; Hogenkamp & Schiöth, 2013; Sugita et al., 2018; Zhu & Hollis, 2015; McCrickerd & F orde, 2017; Nakamichi et al., 2014; Ikeda et al., 2018; Salley et al., 2016; Bellisle, 2020.	Not clinical trials.
Koidis et al., 2018; Perry et al., 1979.	Unretreived article.
Zhu & Hollis, 2014; Zhu et al., 2014; Koidis et al., 2018.	Not fulfill the inclusion and exclusion criteria.
Higgs & Jones, 2013.	Published in a corrected version.
UMIN-CTR, Linoby A.; ICTRP, Schmidt-Lucke C.; UMIN-CTR, Hidaka N.; UMIN-CTR, Miyashita M.; UMIN-CTR, Morillama K.; ClinicalTrials.gov, Bolhuis DP.	RCTs that are ongoing, no preliminary results published.

Table 2. Characteristics of studies included in the systematic review; participants, study information and results. (UW: Underweight-NW: Normal Weight-OW: Overweight - OB: Obese).

Reference	**Participants**				**Study Information**			**Results**			
	n	**Sex M/F**	**BMI (Kg/m²)**	**Age (yr) (Mean ± SD)**	**Study Design**	**Test food**	**Test procedure**	**Effect on food intake**	**Effect on appetite**	**Effect on BMI**	**Effect Hormones & Metabolites**
Andrade et al. (2008)[20]	30	0/30	UW, NW, OW and OB	22.9 ±7.1	Randomized design	Ditalini pasta	Two study conditions: fast (large mouthfuls, consumption as fast as possible, without pauses) and slow (small mouthfuls, with breaks, from 20 to 30 chewing cycles per mouthful)	Significant effect on intake reduction in slow condition	No significant effect	NR	NR
Azrin et al. (2008)[21]	10	0/10	NW	24,3	Reversal experimental design	Lasagna, Chinese food, pizza, macaroni and cheese, pastries, meat, pasta, fish, chips, and corn meal	Each participant received six meals to eat on two different days; three meals with the slow-fast-slow sequence on one day, and three meals with the fast-slow-fast sequence on the other day	NR	Significant effect on appetite reduction in the slow conditions	NR	NR
Bolhuis et al. (2014)[22]	50	11/39	NW	24 ± 2	Randomized, 2-arm, cross-over study, within subjects	Hamburger (soft and hard)/ rice salad (soft and hard)	Two study conditions: lunch ad libitum with hard or soft foods. Dinner ad libitum 5 hours later	Significant effect on intake reduction of the test meal with hard foods. No significant effect. later food intake	No significant effect	NR	NR
Borvornparadorn et al. (2019)[23]	41	17/24	NW and OW	NW: 21.45 ± 1.32 OW: 20.76 ± 1.22	Randomized cross-over design	Ham and cheese on white bread sandwich with 300 mL of water	Two study groups: 15 and 50 chewing cycles per mouthful	Significant effect on intake reduction in condition of 50 chewing cycles	No significant effect	NR	No significant effect on plasma glucose and insulin levels

... continuación Tabla 2.

Reference	Participants				Study Information			Results			
	n	Sex M/F	BMI (Kg/m²)	Age (yr) (Mean ± SD)	Study Design	Test food	Test procedure	Effect on food intake	Effect on appetite	Effect on BMI	Effect Hormones & Metabolites
Cassady et al. (2009)[24]	13	8/5	NW	24 ± 1.8	Randomized, 3 arm, cross-over design	Almonds	Three study conditions: 10, 25 and 40 chewing cycles for each 5g of almonds	NR	Significant effect on appetite reduction in condition of 40 chewing cycles	NR	No significant effect on plasma glucose, ghrelin and PYY Significant effect on the increase of GLP-1 when number of cycles increased
Farooq et al. (2017)[25]	18	15/3	NW and OW	27.7 ± 2.8	Randomized Controlled Trial	Fried rice	Two study conditions: Number of usual chewing cycles of each participant and reduced by 25%	Significant effect on intake reduction in condition reduced by 25%	No significant effect	NR	NR
Ferriday et al. (2016)[26] Study 2	24	12/12	NW	M: 21.2 ± 2.7 F: 24.3± 4.7	Counter balanced, randomized, 4-arm, cross-over design, within subjects, simple size power calculation	Beef stew with dumplings /fish, chips and peas	Consumption of a fixed portion of food in slow or fast condition, followed by a meal ad libitum of the same food or a dessert, and one hour later snack intake ad libitum	Significant effect on intake reduction after slow condition	Significant effect on appetite reduction in slow condition	NR	NR
Ford et al (2009)[27]	106	59/47	OB	Experi mental group: 12.7 ± 2.2 Control group: 12.5 ± 2.3	Randomized controlled trial	Dietary advice provided by a pediatric dietitian, based on the Food Standards Agency "eatwell plate"	Participants were instructed to use a mandometer for a daily meal in order to help them feel "full" after ingesting 300-350 g of food in 12-15 minutes	Significant effect on intake reduction	No significant effect	Significant effect on BMI reduction	Significant effect on HDL-C increase

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Reference	**Participants**				**Study Information**			**Results**			
n	**Sex**	**BMI M/F**	**Age (Kg/m²)**	**Study (yr) (Mean ± SD)**	**Test Design**	**Test food**	**Effect procedure**	**Effect on food intake**	**Effect on appetite**	**Effect on BMI**	**Hormones & Metabolites**
Higgs & Jones (2013)[28]	41	7/34	NW	20.35 ± 2.82	Between subjects experimental design	Sandwich	Three study groups: usual chewing, 10-second breaks between each mouthful and prolonged chewing of 30 seconds before swallowing. Two hours after, a meal ad libitum was served	Significant effect on intake reduction in the condition of chewing 30 seconds 2h after the test food	No significant effect.	NR	NR
Komai et al. (2016)[29] Study 2	10	0/10	NW	20.6 ± 0.6	Randomized, 2-arm, within subjects design	Hamburger, rice and soup	Two study conditions: solid food with 30 chewing cycles per mouthful and soft food without chewing	NR	Significant effect on appetite reduction after solid meal	NR	NR
Labouré et al. (2002)[30] (First Experimental Lunch)	12	12/0	NW	21.5 ± 0.6	Randomized, 5-arm, within subjects design	Soup with two different textures: mixture (inducing long and difficult chewing) and purée (a creamy, smooth soup without necessity of mastication)	Two lunch sessions: one with each food, followed by a dinner ad libitum	No significant effect	No significant effect	NR	No significant effect on plasma glucose levels. Significant effect on the increase in insulin levels with mashed food
Labouré et al. (2002)[30] (Second Experimental Lunch)	12	12/0	NW	21.5 ± 0.6	Randomized, 5-arm, within subjects design	Rusks with three different textures: solid rusk meal, liquid rusk meal, sandwich loaf meal	Three lunch sessions: one with each food, followed by a dinner ad libitum	No significant effect on later food intake	No significant effect.	NR	Significant effect on increase in plasma glucose levels. No significant effect on insulin levels

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Reference	**Participants**				**Study Information**			**Results**			
n	**Sex**	**BMI M/F**	**Age (Kg/m²)**	**Study (yr) (Mean ± SD)**	**Test Design**	**Test food**	**Effect procedure**	**Effect on food intake**	**Effect on appetite**	**Effect on BMI**	**Hormones & Metabolites**
Lasschuijt et al. (2017)[31]	58	14/44	NW (22 ± 2)	23 ± 9	2 × 2 factorial, randomized crossover-design	Strawberry flavored model food gels	Four sessions, in each one an ad libitum portion of one of the four food models was consumed (that varied in hardness and sweetness)	Significant effect on intake reduction with the hardest foods compared to soft ones	No significant effect	NR	NR
Lasschuijt et al. (2020)[32] Study 1	40	40/0	NW (22 ± 2)	24 ± 4	2 × 2 randomized crossover design	Chocolate custard (with caramel sauce or caramel fudge pieces)	Four sessions, in each they were instructed to consume the test food with high OSE-fast ER, low OSE-slow ER, low OSE-fast ER and high OSE-slow ER, as applicable	Significant effect on the intake reduction in the condition high OSE-slow ER compared to low OSE-fast ER	Significant effect on appetite reduction in the conditions of high OSE compared to conditions of low OSE	NR	NR
Lasschuijt et al. (2020)[32] Study 2	20	20/0	NW (23 ± 2)	23 ± 3	2 × 2 randomized crossover design	Chocolate custard (with caramel sauce or caramel fudge pieces)	The tests were the same as in study 1, and included a condition of additional control during which participants did not eat or drink anything	Significant effect on intake reduction in the condition high OSE-slow ER compared to low OSE-fast ER	Significant effect on appetite reduction in the conditions of high OSE compared to conditions of low OSE.	NR	No significant effect on plasma glucose and ghrelin levels. Significant effect on the increase in insulin levels in high OSE-slow ER and on PP in low OSE-fast ER
Li et al. (2011)[33] Study 2	30	30/0	NW and OB	NW: 20.8 ± 0.8 OB: 20.4 ± 0.7	Randomized, 2-arm, within subjects design	Pork pie	Two study conditions: 15 and 40 chewing cycles per mouthful	Significant effect on intake reduction in condition of 40 chewing cycles	No significant effect.	NR	No significant effect on plasma glucose levels. Significant effect on

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Reference	**Participants**				**Study Information**			**Results**			
n	**Sex**	**BMI M/F**	**Age (Kg/m²)**	**Study (yr) (Mean ± SD)**	**Test Design**	**Test food**	**Effect procedure**	**Effect on food intake**	**Effect on appetite**	**Effect on BMI**	**Hormones & Metabolites**
											reduction of ghrelin levels and the increase in CCK levels in the condition of 40 chewing cycles
Martin et al. (2007)[34]	48	22/26	OW and OB	30.7 ± 10.2	Randomized, 3-arm, between subjects design, sample size power calculation	Fried chicken	Two study conditions: Reduced chewing speed (by 50%) and combined speed (normal rate-reduced by 50%).	Significant effect on intake reduction in conditions of reduced speed and combined in men. No significant effect among women	Significant effect on appetite reduction in combined speed condition	NR	NR
McGee et al. (2011)[35]	16	5/11	OW and OB	35.2 ± 2.7	Open-label trial	Moderately hypocaloric diet based on the Dietary Approaches to Stop Hypertension (DASH) plan	A SMART device was made for each participant to use at meals for 4 months, accompanied by a diet plan	NR	Significant effect on appetite reduction	Significant effect on BMI reduction	No significant effect on HDL-C and LDL-C levels
Shah et al. (2014)[36]	70	NR	NW, OW and OB	NW: 33.3 ± 12.5 OW/OB: 44.1 ± 13.0	Randomized crossover design	Mixed meal of vegetable pasta	Two study groups: condition of fast or slow chewing as applicable	Significant effect on intake reduction in slow condition	Significant effect on appetite reduction in slow condition	NR	NR
Smit et al. (2011)[37]	13	5/8	NW and OB	NR	Counter balanced, Randomized	Penne pasta	Two study conditions: 10 and 35 chewing cycles per mouthful	Significant effect on reduction in	No significant effect	NR	NR

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Reference	Participants				Study Information			Results			
n	Sex	BMI M/F	Age (Kg/m²)	Study (yr) (Mean ± SD)	Test Design	Test food	Effect procedure	Effect on food intake	Effect on appetite	Effect on BMI	Hormones & Metabolites
								condition of 35 chewing cycles			
Weijzen et al. (2008)[38]	59	5/54	UW, NW and OW	28.4	2 x 2 (snack food x consumption condition) cross-over design.	Biscuits with chocolate and hazelnut cream filling	Four sessions, two study conditions: (attention/ control), in each session one of the snacks was served in one of the study conditions	No significant effect	NR	NR	NR
Zandian et al. (2009)[39]	47	0/47	NW	21.2	Two groups (decelerated and linear eating rate), within subjects design	Rice, sliced chicken and vegetables	Four study conditions: food intake at 40% of usual time, increased intake (consumption of 40% more foods in the usual time), reduced intake (consumption of 30% less food in the usual time), intake increased by 40% and slowed down (1 minute break for every 60g ingested)	Significant effect on intake reduction in decelerated consumers. Signficant increase in intake in linear consumers	Significant effect on appetite reduction in decelerated consumers. No significant effect on linear consumers	NR	NR
Zhu et al. (2013)[40]	21	21/0	NW and OB	24 ± 1	Randomized cross-over design	Freschetta brick oven fire baked 5-cheese pizza – pasta	Two study conditions: 15 and 40 chewing cycles per mouthful	No significant effect on intake 3h after the test meal	Significant effect on appetite reduction in condition of 40 chewing cycles	NR	Significant effect on the increase in plasma glucose, insulin, GIP, CCK levels and decrease in ghrelin levels in the condition of 40 cycles
Zhu et al. (2014)[41]	47	24/23	NW, OW and OB	NW: 22.2 ± 1.3 OW: 23.1 ± 1.7	Randomized cross-over design	Totino's cheese pizza rolls	The number of chewing cycles was increased to 150% and 200%	Significant effect on intake reduction in the 200%	No significant effect	NR	NR

... continuación Tabla 2.

Reference	**Participants**				**Study Information**			**Results**			
n	**Sex**	**BMI M/F**	**Age (Kg/m²)**	**Study (yr) (Mean ± SD)**	**Test Design**	**Test food**	**Effect procedure**	**Effect on food intake**	**Effect on appetite**	**Effect on BMI**	**Hormones & Metabolites**
				O: 25.3 ± 1.8				condition			
Zijlstra et al. (2010)[42]	106	45/61	NW	24 ± 7	randomized cross-over experiment	Luncheon meat, vegetarian meat replacer and chewy candy	Each test food had a soft and a hard version, in six sessions they were instructed to eat the test products ad libitum	No significan effect	No significant t effect	NR	NR

DISCUSSION

The aim of this systematic review was to analyze the available evidence regarding the effect of chewing behavior modification on the parameters that contribute to obesity. For this, 23 articles that intervened in the chewing behavior of the participants and analyzed the variation in intake levels, appetite, BMI and satiety-related hormones and metabolites. Of these, most determined that the reduction in ER, increase in OSE and increase in the number of chewing cycles achieved a significant reduction in the amount of food ingested as well as appetite both during the intervention and hours later.

By contrast, a single study[25] reported that food intake was significantly lower with a smaller number of chewing cycles. We infer that the result was due to the methodology used, since the participants were told when to stop eating (on fulfilling 75% of chewing cycles), and therefore they ate less food than in the 100% sessions.

It has been described that the dorsal vagal complex in the medulla oblongata and the parabrachial nucleus in the projection play a key role in satiation by processing the information about the energy state on four different levels, the first being the detection of metabolites circulating and hormones released by the peripheral organs[4,9]. Among these, we found plasma glucose, insulin, CCK, GLP-1, PYY, GIP, PP and ghrelin. The first seven have anorexigenic effects, i.e., they participate as appetite suppressors, physiologically inhibiting food intake, thus their levels are high after meals and low in fasting conditions[4,9,43]. By contrast, ghrelin, a gastrointestinal peptide hormone, has orexigenic or stimulating effects on the appetite. The secretion of this hormone is prominent in fasting and falls after ingestion[44,45].

The sensory signals of foods, such as flavor, texture and sight, travel to the encephalic trunk producing a cascade of pre-absorbent physiological responses, called cephalic phase responses (CPR). These involve the increase in saliva production, increase in intestinal mobility, secretion of gastric and pancreatic juices, and the secretion of hormones like insulin, PP and ghrelin. This last one presents a marked increase pre-prandially and falls post-prandially. Such hormones play an important role in satiation, enabling the control of food intake. CPR remain in continuous stimulation until the last mouthful is ingested[5,9,46]. Once the food passes to the stomach and continues its digestion process a series of mechanisms from the post-ingestion phase are added to the CPR, among which it is important to emphasize gastric distension and the secretion of hormones like CCK, PYY, GLP-1, and others, that play an important role in satiety, i.e., at the beginning of the following meal. The combination of the CPR and post-ingestion responses is crucial for the adequate regulation of food intake[4,9,5]. Kokkinos et al. (2010)[12] discovered that the speed at which food is ingested directly affects the responses of the satiety-related intestinal hormones, demonstrating that eating at a physiologically moderate rate leads to a stronger anorexigenic response than eating more quickly, which produces a much weaker anorexigenic response. On this basis, emphasis is placed on the importance of detecting changes in the plasma levels of satiety-related hormones and metabolites when intervening in chewing behavior. The selected studies that extracted blood samples evaluated the changes in these levels, obtaining varying results. For metabolites and hormones with an anorexigenic effect, a significant increase was observed in most studies after performing a greater number of chewing cycles or oral processing time compared to the opposite conditions. However, in one study[32], it was observed that PP levels were significantly lower in the group with a slow ER and a high OSE compared to the group with fast ER and low OSE, which did not agree with authors' initial hypothesis, which posited that a food with chewing versus one without chewing would increase anorexigenic hormones such as insulin and PP. This result may be because consuming a soft food, with a low OSE, produces faster gastric emptying than when consuming a more solid food. This would mean that the ingested foods reach the duodenum faster and produce a sharper increase in anorexigenic hormone responses[5,47]. On the other hand, the study by Laboure et al. (2002)[30] reported higher insulin levels after eating mashed food (without needing to chew) than eating the same food as a solid (which requires chewing). These results are also contrary to the initial theory, but this may be justified in the same way as the previous study, i.e., a greater insulin secretion after mashed food could be due to a greater glucose absorption, because gastric emptying is faster for a liquid than for a solid. Research is still lacking to support this explanation, and the analysis of these results emphasizes the need for more studies that analyze the interaction between OSE, gastric emptying and hormone responses in greater depth.

Ghrelin was analyzed in four studies, in two of which its plasma levels fell after a greater number of chewing cycles compared to when fewer cycles were performed[33,40], and in two studies it stayed steady with no significant variations[24,32]. It has been suggested that these results could be because, as chewing increases, in any of the components of OSE, such as duration, intensity, food texture, etc., there is a greater accessibility to the nutrients for absorption. This increased bioaccessibility is important for the stimulation of the pre-absorption mechanisms, like those involved in the previously explained neurohormonal regulation of food intake[9,48]. Thus, it is shown that interventions in chewing behavior physiologically affect appetite modulation, and therefore food intake, and thus the success of these interventions is no longer justified only with subjective results on appetite, but rather there is also a physiological justification that objectively substantiates their inclusion in treatments against obesity. Nevertheless, studies are needed that assess these same variations over a more prolonged period of time in order to observe whether these changes can be maintained over a sustained period.

The qualitative analysis of the analyzed studies demonstrates that interventions in the chewing process can carry with them multiple benefits in the treatment of obesity, with reductions in intake levels, appetite and beneficial modifications in gastrointestinal hormone levels. Two studies also reported a drop in BMI over a longer period of time[27,35].

Two studies that had a long follow-up (4 and 18 months), McGee et al. (2011)[35] and Ford et al. (2009)[27], achieved successful results both for weight loss and eating behaviors, such as lifestyle changes, chewing speed, awareness of portion size and satiety. In addition, these two studies analyzed the possible variations in cholesterol levels together with high-density lipoproteins (HDL-C) during the study period. It is known that higher levels of HDL-C are linked to lower cardiovascular risk, and that an increase in HDL-C through changes in lifestyle has positive effects on health48. Comparing HDL-C levels throughout the treatment, McGee et al. (2011)[35] observed no significant differences, unlike Ford et al.(2009)[27], who reported that HDL-C levels increased significantly at the end of the treatment, thereby demonstrating that changes in eating behavior over a long period of time does indeed bring with it a set of overall health benefits. These results justify interventions at the clinical level and future studies that endeavor to study the role of chewing behaviors in the different factors that contribute to obesity.

The limitations present in the studies show that most of the experiments were conducted in laboratory surroundings, which may not be applicable to real life. Additionally, in some studies only one test food was used, which does not reflect a full daily intake. In terms of the sample size of the studies, in most no sample size calculation was performed; it is therefore advisable to include this in future studies so that a representative sample of the population can be employed. Finally, the follow-up period was very short, less than in a month in most of the analyzed studies. This is an important limitation, since the studies mainly evaluated immediate results, which does not allow for reflection on possible behavioral changes sustained over time. Long-term studies are required to evaluate these effects and determine the applicability of the results in different populations over more prolonged periods.

As far as the quality of the evidence studied, most of the studies were evaluated with an overall low risk of bias; however, almost all had a high or uncertain risk in the blinding of participants and personnel. Due to the nature of most of the studies, it was impossible to blind both the clinicians and participants, since the clinicians were responsible for manipulating the speed, number of chewing cycles, or other variables analyzed according to the study. This characteristic can affect the results directly, mainly in the subjective evaluations of appetite, since the fact that the participants had knowledge of the study condition, it could directly affect the response they give for this parameter. However, the objective and measurable variables, such as amount of food ingested, BMI and hormonal analysis are not affected by this situation.

The results obtained in this systematic review agree with other reviews. Miquel-Kergoat et al. (2015)[17], after analyzing 17 studies, concluded that prolonged chewing significantly reduces intake levels and self-reported hunger; however, like us, they justify the need to continue conducting experimental studies on this topic to deepen understanding of these connections and to learn the effects of such interventions over a prolonged period so as to generate quality evidence that serves as the foundation to design interventions that complement the treatment of obesity. Krop et al. (2018)[18], after analyzing 42 studies, also determined that the manipulation of chewing behavior reduces the subjective appetite and food intake, and they also justify the need to include in such studies an analysis of the influence of the incorporation of saliva and oral lubrication on the appetite and food intake scores, which to date has not been studied in depth and is considered an important factor in the eating behavior interventions.

CONCLUSION

Current available evidence seems to indicate that modifications in chewing behavior, such as reduction in ER, increased OSE, modification of the texture of foods, and an increase in the number of chewing cycles, are effective at reducing food intake, subjective appetite and improving plasma levels of satiety-related hormones and metabolites. In addition, it is shown that these interventions reduce BMI in the long term.

New clinical trials are needed, in which the shortcomings present the current intervention studies are improved, such as sample size calculation, longer follow-up periods, studies in surroundings outside of the laboratory and with more common foods.

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