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The Problem of Appetite Loss After Major Abdominal Surgery

A Systematic Review

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Objective: To systematically review the problem of appetite loss after major abdominal surgery.

Summary of Background Data: Appetite loss is a common problem after major abdominal surgery. Understanding of etiology and treatment options is limited.

Methods: We searched Medline, Cochrane Central Register of Controlled Trials, and Web of Science for studies describing postoperative appetite loss. Data were extracted to clarify definition, etiology, measurement, surgical influence, pharmacological, and nonpharmacological treatment. PROSPERO registration ID: CRD42021224489.

Results: Out of 6144 articles, we included 165 studies, 121 of which were also analyzed quantitatively. A total of 19.8% were randomized, controlled trials (n = 24) and 80.2% were nonrandomized studies (n = 97). The studies included 20,506 patients undergoing the following surgeries: esophageal (n = 33 studies), gastric (n = 48), small bowel (n = 6), colon (n = 27), rectal (n = 20), hepatobiliary (n = 6), and pancreatic (n = 13). Appetite was mostly measured with the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ C30, n = 54). In a meta-analysis of 4 randomized controlled trials gum chewing reduced time to first hunger by 21.2 hours among patients who had bowel surgery. Other reported treatment options with positive effects on appetite but lower levels of evidence include, among others, intravenous ghrelin administration, the oral Japanese herbal medicine Rikkunshito, oral mosapride citrate, multidisciplin-ary-counseling, and watching cooking shows. No studies investigated the effect of well-known appetite stimulants such as cannabinoids, steroids, or megestrol acetate on surgical patients.

Conclusions: Appetite loss after major abdominal surgery is common and associated with increased morbidity and reduced quality of life. Recent studies demonstrate the influence of reduced gastric volume and ghrelin secretion, and increased satiety hormone secretion. There are various treatment options available including level IA evidence for postoperative gum chewing. In the future, surgical trials should include the assessment of appetite loss as a relevant outcome measure.

Keywords: appetite loss, major abdominal surgery, quality of life, systematic review

(*Ann Surg* 2022;276:256–269)

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Reprints will be not available from the authors.

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Michael Haselbeck-Koebler and Johanna M. Brandenburg screened titles, abstracts and full text articles, extracted the data, and wrote parts of manuscript.

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Joe J. Simon PhD and Hans-Christoph Friederich MD analyzed the data on definitions, etiologies and measurement options, contributed additional relevant literature, and contributed to writing of the respective paragraphs.

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All authors critically reviewed and approved the manuscript. All authors gave final approval of the version to be published.

The other authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

ISSN: 0003-4932/22/27602-0256

DOI: 10.1097/SLA.0000000000005379

"Doctor, I have lost my appetite." This is a complaint every surgeon faces daily in their clinical practice. Whether in the outpatient clinic, upon initial contact with a gastric cancer patient undergoing evaluation for surgical treatment, on ward rounds during the days after colorectal surgery, or at follow-up visits months or even years after esophageal surgery, when patients have been cured of their cancer but still suffer from the consequences of major surgical changes to their gastrointestinal tract, appetite loss after major abdominal surgery is a pervasive and quality-of-life altering problem.

Appetite loss, a common occurrence in nonsurgical diseases, can be influenced by many conditions: affective disorders such as major depression are commonly associated with changes

in food intake and appetite,[1] with 48% of patients reporting depression-related decreases in appetite.[2] Furthermore, reduced appetite is a hallmark feature in anorexia nervosa.[3] Cancer,[4] infections,[5] chronic kidney disease,[6] or inherited disorders such as cystic fibrosis[7] are also known to reduce appetite. Furthermore, aging is associated with a reduction in appetite,[8] which can cause malnutrition and increased overall morbidity.[9]

In surgical practice, unintentional appetite loss is a multiface-ted problem with varied consequences. Low preoperative food intake increases the risk of postoperative complications.[10] Pretreatment appetite loss has also been identified as an important prognostic factor for patients with gastroesophageal cancer.[11] The nutritional state of patients undergoing liver transplantation represents an independent predictor of morbidity and mortality.[12] Adequate preoperative food intake improves the wound healing response in patients undergoing major abdominal surgery.[13] After surgery (even following enhanced recovery programs for colorectal surgery), up to 55% of patients suffer from partial or total appetite loss 2 weeks post op.[14] Also, significant weight loss as a consequence of appetite loss has been well documented and is especially common after upper gastrointestinal surgery.[15] If postoperative appetite loss leads to malnutrition, this adversely impacts survival, complications, and quality of life.[16] After nonabdominal surgery such as primary joint replacement, it takes up to 4 weeks for patients to recover their preoperative appetite.[17]

In contrast, appetite loss is intentional in metabolic surgery and the mechanisms that result in the desired appetite reduction after metabolic surgery are likely similar to the detrimental effects on appetite after major abdominal surgery, especially in oncologic patients. Already in 1967, when Mason and Ito for the first time described gastric bypass as "an operation exactly like Billroth II gastric resection except that nothing is removed," they made intentional use of postoperative appetite loss.[18] By then they already suspected that the effects on weight may also be mediated by a change in the secretion activity of the pancreas.[19] Today, 5 decades later, appetite changes after metabolic surgery, including the altered reward value of food, have been investigated in numerous studies. Attenuated appetite may be the key to weight loss and weight loss maintenance.[20] Subjective changes in appetite, taste, and smell, which have been reported routinely after Roux-en-Y gastric bypass and sleeve gastrectomy, might initially be caused by a disturbance in the homeostasis of ingestive processes.[21,22] Furthermore, increased levels of appetite suppressing hormones glucagon like peptide-1 (GLP-1) and Peptide YY (3-36) contribute to appetite loss after metabolic surgery.[23] In general, appetite loss is one of the aims of metabolic surgery and is, therefore, not considered a problem among those patients.

Nonintentional appetite loss, however, is a surgical problem, because it is neither easy to measure nor easy to treat. Appetite relates to subjective experience and the perception of physical and hedonic hunger. Therefore, similar to pain, appetite assessment is highly subjective. However, the consequences of appetite loss, such as malnutrition, weight loss, or a decrease in serum albumin, are all amenable to objective assessment. Methods of feeding patients who are unable to eat, including nasogastric tube, percutaneous gastro-stomy, and parenteral nutrition, may prevent postsurgical weight loss but they are also rather unpleasant and fail to relieve distressing food intake sensations.[24] To avoid postoperative malnutrition caused by decreased food intake, surgeons urge their patients to eat more, but that does not solve the underlying problem of appetite loss.

Although some authors have investigated the nutritional implications of treating patients after gastric or esophageal surgery,[25] a comprehensive and systematic overview of unintentional appetite loss after major abdominal surgery is still lacking.

This paper systematically reviews the literature on the problem of appetite loss after major abdominal surgery. To identify the types of evidence available, to analyze knowledge gaps, and to provide the practicing surgeon with clinically relevant recommendations, we aimed to answer the following questions:

- Definition: What is appetite?
- Etiology: Where does appetite loss after major abdominal surgery come from?
- Measurement: How can appetite loss be measured?
- Surgical Influence: How does major abdominal surgery influence appetite?
- Treatment: How can postoperative appetite loss be treated?

METHODS

This review follows the recommendations of the Cochrane Handbook for Systematic Reviews and Interventions[26] and is in line with the preferred reporting items for systematic reviews and meta-analysis statement.[27] A review protocol was developed a priori and registered in PROSPERO under the number CRD42O21224489.

Eligibility Criteria

Studies included in this systematic review were chosen according to patient, intervention, control, outcome, study type (PICOS) criteria, with patients of any sex or gender over the age of 18 who underwent major abdominal surgery (P) meeting our criteria. Major abdominal surgery was defined as operations requiring a gastrointestinal anastomosis or involving bowel resection or parenchymal resection of the liver or pancreas. All interventions (I) or observations with or without control (C), studying the definition, etiology, measurement, or treatment of the outcome of unintentional postoperative loss of appetite (O) were included. All study types (S) were accepted.

This review excluded publications on altered appetite without previous surgery, on bariatric or metabolic surgery (because loss of appetite is an expected and intended outcome in this case), and those published in a language other than English.

Systematic Literature Search

Medline (via Pubmed), the Cochrane Central Register of Controlled Trials, and Web of Science were searched.[28] The last database search was performed on November 30th, 2020. Additionally, following discussions with experts in the fields of major abdominal surgery (M.W.B., T.H., P.P.), metabolic surgery (A.T.B., B.M.-S.), anesthesiology and palliative care (J.K.), nutritional medicine (P.P.), clinical pharmacology (D.S.), and internal medicine and psychosomatics (J.J.S., H.-C.F.), other studies relevant to the problem of appetite loss after major abdominal surgery were identified.

The search was conducted using a combination of medical subject headings and free-text words. Search strategies for all bibliographic databases can be found in Supplemental Digital Content 1, http://links.lww.com/SLA/D654.

Study Selection

Two authors (M.H.-K. or J.M.B.) screened titles and abstracts for relevance. Positively evaluated reports were further

screened by M.W., who provided an independent decision on whether to perform full-text screening. The same procedure was then followed for full-text screening, to determine which studies were eligible for inclusion in the review.

Data Collection Process

The data were extracted using a predefined form (available upon request). After a pilot phase with 10 articles, the form was further refined and data extraction was performed by either M.H.-K. or J.M.B. Uncertainties during data extraction were discussed and resolved in discussion with M.H.-K., J.M.B., and M.W.

General information (year of publication, first author) and study characteristics (randomization, number of patients enrolled, number of patients with appetite measured) were also noted.

Definitions of appetite and appetite loss were extracted to answer the question "What is appetite loss after major abdominal surgery?" Mechanisms of appetite loss were extracted to answer the question "Where does it come from?" Methods of measuring appetite or appetite loss, and the timing of appetite measurement in relation to the operation, were extracted to answer the question "How can postoperative appetite loss be measured?"

Type of operation (esophagus, gastric, small bowel, colon, rectum, hepatobiliary, pancreas, other/multiple) and operative procedure were extracted to answer the question "How does major abdominal surgery influence appetite?"

To answer the question "How can postoperative appetite loss be treated?" drug name, dosage, and efficacy (for studies examining the pharmacological treatment of appetite loss) or the type, description, and efficacy of nonpharmacological treatments were extracted.

Risk of Bias and Certainty in Evidence

Because the problem of appetite loss after major abdominal surgery itself has not yet been systematically investigated, and to identify and analyze knowledge gaps, we decided to include all of the available studies in our analysis. Where quantitative data synthesis was performed, we assessed risk of bias with RoB 2, the revised version of the Cochrane risk-of-bias tool.[29] This tool includes 5 risk of bias domains, namely bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of reported results. Risk of bias data was visualized with the R-package robvis.[30,31]

Summary Measures and Synthesis of Data

Bubble plots were created for observational, surgical strategy, and nonsurgical treatment studies, to map them by type of operation and according to the time between operation appetite measurement. Within the bubble plots, trial sample size was expressed by bubble size and randomization by a color code. Quantitative data synthesis was performed only for trials investigating the influence of gum chewing, because all other topics among the studies in this review proved too heterogenous. For continuous data (time to first hunger), weighted mean differences and their associated 95% confidence intervals were calculated using an inverse-variance model. If not reported, mean and standard deviation were estimated.[32] A 2-sided level of significance below 5% was considered statistically significant. Statistical heterogeneity among trials was evaluated by means of the I^2 statistic. Bubble plot visualization[33] and meta-analysis[34] were performed with R statistics.[30]

RESULTS

The results of this systematic review include information about the definitions, etiologies, measurement, and treatment of appetite loss after major abdominal surgery (Fig. 1).

Study Selection

The literature search yielded 6144 articles. Of these, 5894 were excluded after title and abstract screening. Full-text-screening of the resulting 250 articles was performed, and another 85 were then excluded. Reasons for exclusion included

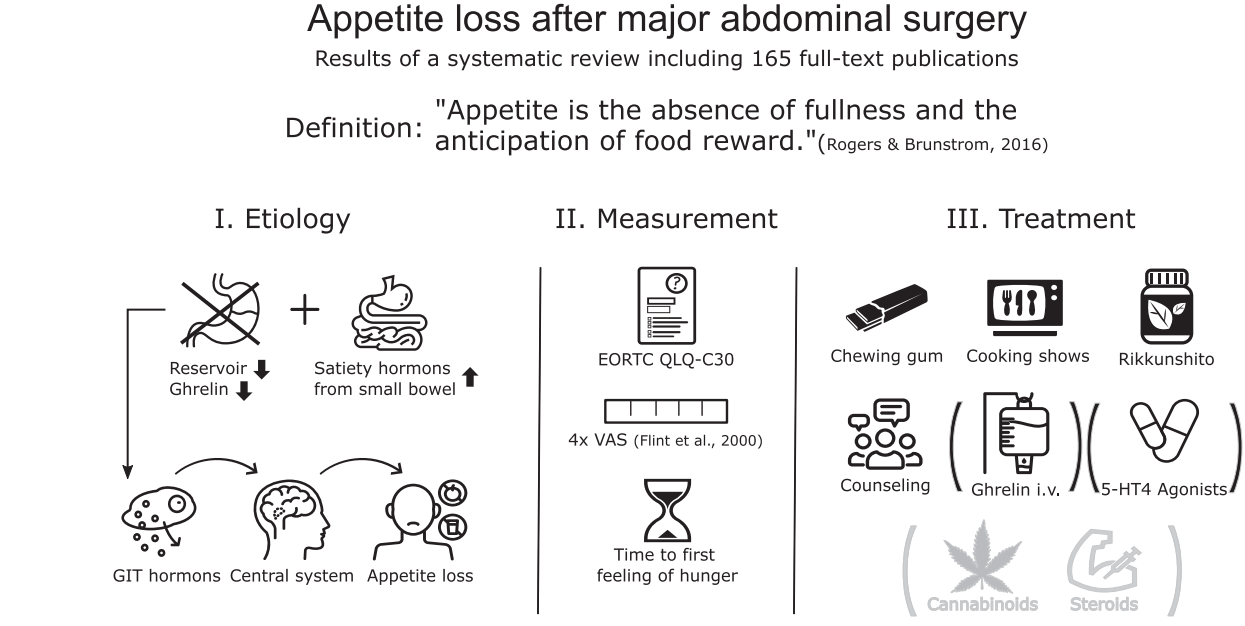

FIGURE 1. Graphical summary of results.

no reporting of appetite (n = 14), conference abstract (n = 10), no surgery (n = 3), trial registration with trial results in a separate publication or no trial results available (n = 16), literature review without additional information (n = 6), case report (n = 1), poor article quality (n = 2), no full-text article available (n = 20), full article not available in English (n = 5), animal study (n = 1), metabolic surgery (n = 2), and duplicate (n = 5). Ultimately, a total of 165 studies were included in the qualitative analysis, with 121 studies of these also included in the quantitative analysis. The complete screening and selection process is presented in Figure 2.

Study Characteristics

Of all studies included in the quantitative analysis (n = 121), 19.8% were randomized controlled trials (n = 24) and 80.2% were nonrandomized studies (n = 97). In total, the studies comprised n = 20,506 patients. Appetite was measured for 86.8% of patients (n = 17,791). The most common type of surgery was gastric surgery (n = 48). Figure 3 gives an overview of the distribution of studies across different types of surgery. Figure 4 gives an overview of the time span between surgery and postoperative appetite measurement, depending on operation type. Separate bubble plots are displayed for studies merely observing appetite loss after major abdominal surgery, studies comparing different surgical strategies, and those investigating treatment options. This mapping strategy identifies overall evidence gaps in our knowledge of appetite loss after major abdominal surgery.

Definition: What is Appetite?

Rogers and Brunstrom define appetite as "the absence of fullness and the anticipation of food reward." More specifically, they refer to the absence of fullness in the upper gastrointestinal tract along with the anticipation of the pleasure of eating or the reward derived from food intake.[35]

From a physiological perspective, Davis et al described 4 phases in normal appetite signaling. These phases include the gastric motility phase, mediated by the vagal afferents, the postabsorptive phase, mediated by the duodenal release of the hormone cholecysto-kinin binding to vagal receptors, the metabolic phase, with glucose and insulin released from the liver and leptin is released from adipocytes, and the ileal phase, with the release of GLP-1.[36] Thus the complex interaction of different hormones underlies the feeling of appetite; for example, ghrelin and motilin accelerate gastric emptying and increase appetite, whereas gastric inhibitory peptide, GLP-1, peptide YY, glucagon, and amylin delay gastric emptying and thereby induce satiety.[37] The "appetite hormone" ghrelin is detected in the stomach and in the hypothalamic arcuate nucleus and regulates energy homeostasis like the appetitive response to food cues.[38] Soon after its initial discovery,[39] animal studies described ghrelin's strong effect as an appetite stimulant in rats.[40] Although numerous additional effects of ghrelin on humans have been described,[41] its main role remains that of appetite regulation.

Apart from hormonal influence within the gastrointestinal tract, the hypothalamus, the brain's central control region responsible for appetite regulation, is also closely connected to higher-order neural circuits involved in food reward, affect, and memory processing. Hedonic hunger, for example, can increase the desire to eat, even in the absence of physiological hunger. Given the multifactorial etiology of appetite, the biological control of appetite still poses several open research questions resulting in "a daunting complexity."[42]

Etiology: Where Does Postoperative Appetite Loss Come From?

In contrast to intentional appetite loss after metabolic surgery, the focus of this review is the problem of unintentional postoperative appetite loss. A number of studies have investigated the negative psychological and physiological effects of major abdominal surgery on appetite.

Psychology

Regarding the psychological perspective on postoperative appetite loss, Wainwright et al performed in-depth interviews with patients after esophagectomy. These patients experienced surgery as a bodily disruption leading, among other effects, to a loss of appetite with appetite either reduced or completely absent for several weeks or longer after surgery. They felt like their body did not tell them when to eat, as if "the pathway between stomach and the brain had literally been cut."[43] There is a lack of studies addressing psychological factors in postoperative appetite loss, and the interplay between psychological and physiological factors.

Ghrelin

From the neurophysiological perspective, the hormone ghrelin plays a central role in appetite regulation. It also plays a major role in appetite loss after gastrectomy, because ghrelin is produced in the fundic gland of the stomach.[44] A number of studies have investigated postoperative changes in ghrelin levels. Koizumi et al reported a significant increase in appetite among patients treated with total gastrectomy from 1 month to 1 year after the operation, and that this increase was accompanied by a recovering ghrelin level of up to 57% of the preoperative baseline.[45] In this context, however, appetite and ghrelin levels showed only a weak positive correlation. In a study with a median time of 6 years after subtotal or total gastrectomy, ghrelin plasma levels were still lower than in healthy controls before and after a test meal. Furthermore, healthy controls experienced a transient decrease in ghrelin plasma levels, whereas gastrectomy patients did not. There was no relationship between ghrelin level and appetite variations.[46] In contrast, Jeon et al reported a 43% decrease in ghrelin plasma level but no change in appetite 1 year after subtotal gastrectomy.[47] In a second study, Jeon et al found a rapid compensatory mechanism after two-thirds distal gastrectomy. Total ghrelin levels decreased after surgery, with a nadir at 70% 1 hour after surgery, while the active form of ghrelin increased to 135% of preoperative values. After 7 days, overall levels of ghrelin returned to 95% of their preoperative values, whereas the level of active ghrelin decreased from 135% to 111% of preoperative values.[48] Another study supported the finding that subtotal gastrectomy patients experienced less of a decline in ghrelin levels immediately after surgery than total gastrectomy patients did. Also, in the long term, their ghrelin levels eventually returned to normal values, whereas those of total gastrectomy patients did not.[49] Seven days after the operation, ghrelin plasma levels decreased by 37% in subtotal versus 47% in total gastrectomy for cancer. Furthermore, ghrelin levels were lower in tumor tissue than in healthy gastric tissue.[50] Thus, the preservation of at least parts of the stomach may result in a lower decline of ghrelin levels and appetite loss. Furthermore, Kim et al hypothesize that the observed reduced appetite loss after vagus preserving distal gastrectomy may be linked to changes in ghrelin production and improved motility of the gastric remnant.[51] However, while it is suspected that

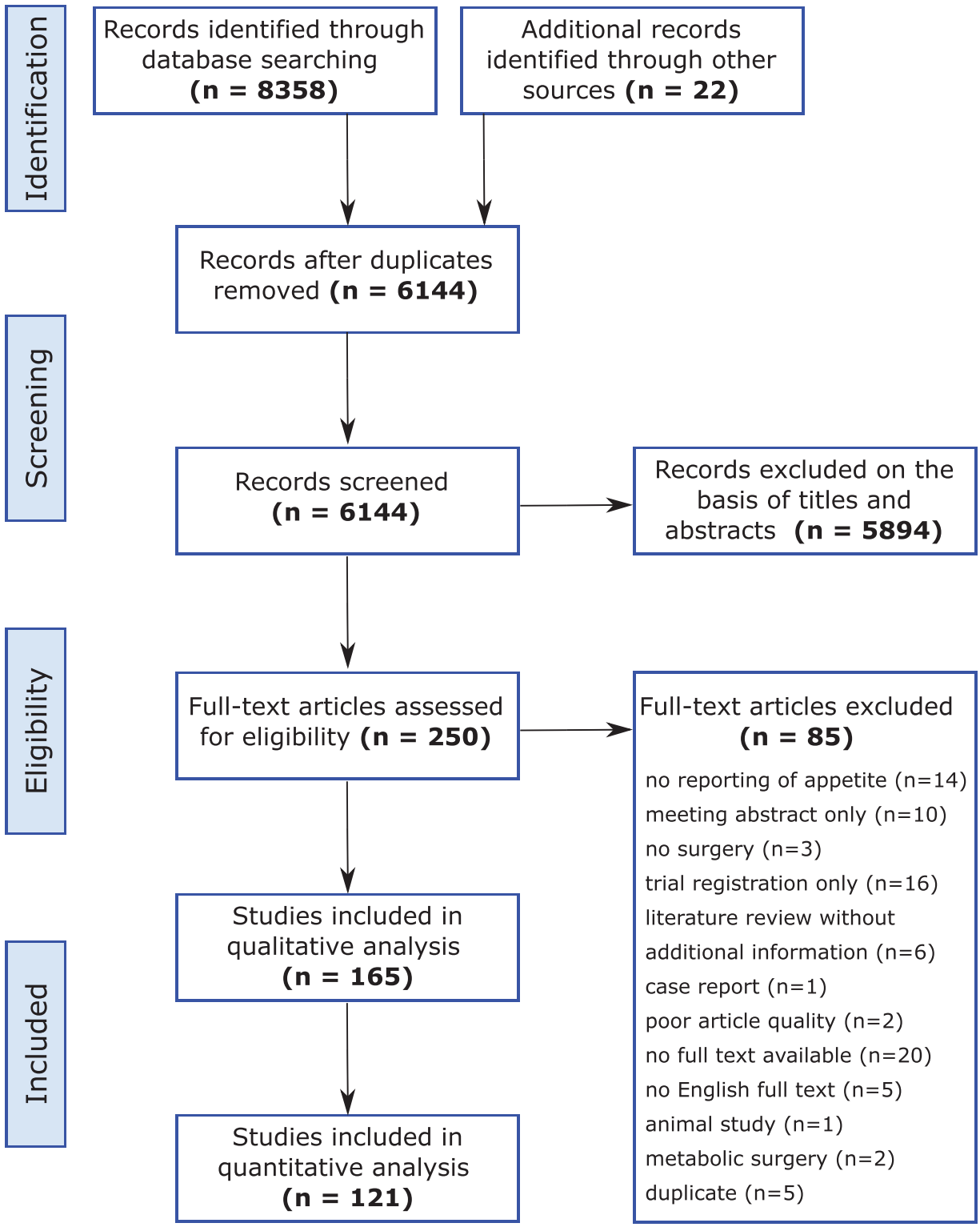

FIGURE 2. PRISMA flow chart. PRISMA indicates preferred reporting items for systematic reviews and meta-analysis.

vagotomy damages normal ghrelin function, this interaction is not fully understood.[44]

The abovementioned positive influence of stomach preservation is in line with findings related to ghrelin changes after esoph-agectomy with gastric reconstruction. This procedure resulted in a reduction of 50% in ghrelin plasma levels, compared to reductions of 88% in total gastrectomy, 50% in two-thirds distal gastrectomy, and no change in colectomy when

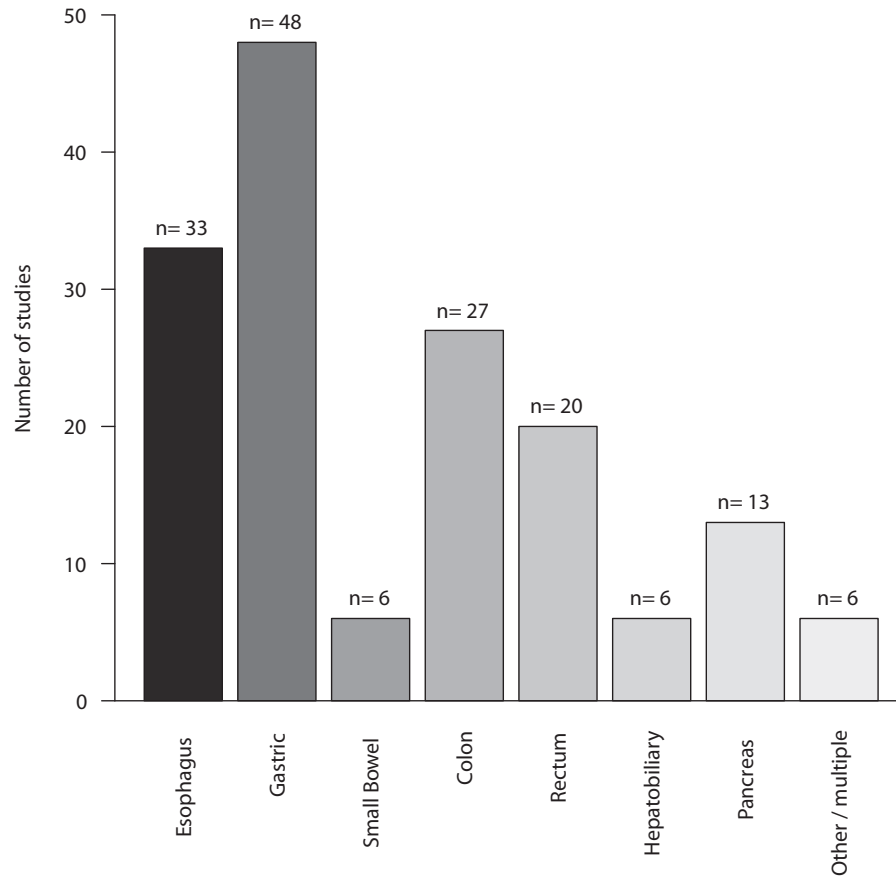

FIGURE 3. Number of studies plotted by type of operation.

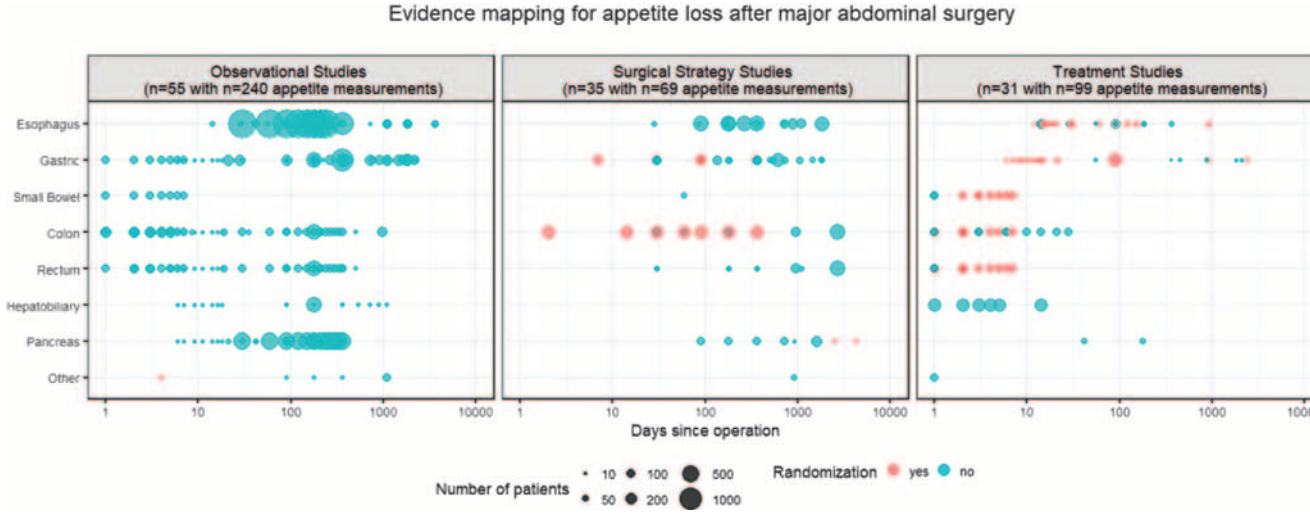

FIGURE 4. Evidence mapping for appetite loss after major abdominal surgery. Studies are mapped by time between operation and appetite measurement (x-axis with log 10 scale) and by type of operation (y-axis). Within the bubble plots, the number of patients with appetite measured is expressed by bubble size and randomization is expressed by a color code. Preoperative appetite measurement was performed in 45 studies (not displayed). If appetite was measured postoperatively more than once in a study or for different surgery types, all measurements are depicted separately, with the patient number for the whole study. If an interval instead of a fixed value of days since operation was stated in the study, the mean is displayed. If mean was not stated, median is displayed. If only a timeframe with 1 boundary (eg, more than 6 years) was stated, this boundary (eg, 6 years) is displayed. If neither was presented, the study is not displayed.

measurements were taken 3 and 7 days after surgery. In longer-term postoperative follow-up, ghrelin level is positively correlated with time from operation, and was even higher than in a control group of preoperative cancer patients without prior weight loss 3 years after surgery.[52] Koizumi et al found that both appetite and ghrelin plasma levels decreased 1 month after esoph-agectomy, with both recovering approximately 1 year postopera-tively. Appetite and ghrelin plasma levels showed a strong positive correlation.[53]

Satiety Hormones and Bowel Motility

Whereas reduced ghrelin levels may cause appetite loss, it may also be caused by an exaggeration of satiety hormones. Dehes-tani and le Roux reviewed the role of the small bowel in unintentional postoperative weight loss. They describe the rapid progress of food into and through the small bowel after upper gastrointestinal surgery as a cause leading to the adaptation of small bowel mucosa and increased secretion of satiety gut hormones such as GLP-1 with a similar effect on satiety caused by bile entering the small bowel faster. A change in gut microbiota may also lead to faster satiation.[15] Preserving the duodenal passage may also result in more normal (rather than increased) levels of the appetite suppressing hormone cholecystokinin.[54]

Reduced bowel motility may be another source of appetite loss. Tomita et al found that the absence of interdigestive migrating motor complex phase III, that is, a group of contractile waves of the gastrointestinal tract migrating in an oral-anal direction during fasting, correlated highly with appetite loss after gastric surgery. Where interdigestive migrating motor complex phase III was present, patients reported almost no loss of appetite. Its absence correlated with appetite loss in the majority of patients. Tomita et al concluded that prokinetic agents, which stimulate gastrointestinal movements, may improve postoperative symptoms.[55,56]

Measurement: How can Appetite Loss Be Measured?

Appetite and appetite loss are subjective sensations, similar to pain. Thus appetite loss is a vastly different problem than surgical complications, such as delayed gastric emptying. The latter can be measured objectively, by nasogastric tube output, or by scintigraphy. Appetite loss is mainly assessed via self-report, which is prone to subjective distortion.

By far the most commonly reported measurement method of appetite loss is the quality of life questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30, n = 54 studies). This questionnaire is a standardized instrument for clinical trials in oncology and has been translated into various languages and validated in multicultural research settings.[57] It consists of 30 items and is composed of multi-item scales and single items and reflects multiple dimensions of quality of life. Patients need about 11 minutes to fill out the questionnaire. Seven items ask binary (yes/no) questions about physical functions. Twenty-one questions measure symptom occurrence over the past week, on a 4-point Likert scale with the options "not at all," "a little," "quite a bit," and "very much." Question 13 addresses appetite by asking "Have you lacked appetite?." Two questions ask about general quality of life on a 7-point Likert scale from "1 – very poor" to "7 – excellent." In contrast, other standardized questionnaires can measure appetite loss, but have rarely been used to measure appetite loss within the studies included in this review. Examples include different versions of the Functional Assessment of Cancer Therapy Questionnaire (n = 4), the Edmonton Symptom Assessment System (n = 4), the MD Anderson Symptom Inventory (n = 2), the Korenaga-Score (n = 2), and Nottingham Health Profile, JenAbdo-men-CF and Symptom Distress Scale (n = 1 each).

Another commonly used and more precise method of measuring appetite (loss) is the visual analog scale (VAS). Although a number of studies have utilized custom VAS measurements without validation of the measurement instrument (n = 14), Flint et al published a validated appetite measurement method.[58] Their method is especially suited to monitoring short-term changes in appetite before and after meals. A VAS of 100 mm length with words anchored at each end for the most negative and positive ratings was used. Appetite was thereby measured in different dimensions, that is, hunger ("How hungry do you feel?"), satiety ("How satisfied do you feel?"), fullness ("How full do you feel?"), and prospective food consumption ("How much do you think you can eat?"). This method, which was also adopted by Kamiji et al, allows for a more differentiated assessment of appetite change after surgery.[59]

Additionally, multi-dimensional approaches to appetite measurement, such as that of Flint et al, reflect another challenge: the difficulty of distinguishing between hunger and appetite. Some authors use these terms synonymously, while others only measure "hunger" (especially when employing "time to first feeling of hunger" as an endpoint for returning bowel function).[60] For the purposes of this review, we consider "hunger" and "appetite" to be equivalent, as only 1 study (Flint et al[58]) differentiates between the 2.

Few studies explore quality of life in surgical patients by means of semi-structured in-depth interviews. Burden et al identified "appetite swings" as a primary theme in colorectal surgery patients who were interviewed about their food and nutrition experiences.

However, they did not measure appetite, but performed a qualitative analysis of themes that patients self-identified as important.[61] In an attempt to provide a conceptual framework for the short-term measurement of quality of life when comparing laparoscopic and open abdominal surgery, Urbach et al identified appetite loss as an important symptom of postoperative visceral dysfunction.[62]

Table 1 gives an overview of methods for the measurement of appetite or appetite loss used by the studies included in this systematic review. One limitation of previous research is that appetite has largely been assessed via simple screening questions that rarely differentiate between physical, gustatory, and hedonic aspects of appetite and food intake. Furthermore, because the amount and type of food was not assessed, further research should also include other measurements, such as a 24-hour recall of food intake or the use of a food diary, which might provide complementary details.

Regarding digitalization methods, Sun et al were able to prove that wireless data collection is feasible. In their study, patients responded to online surveys regarding quality of life, including appetite status, at a satisfactory rate of 65% to 75%.[63] These participation levels are comparable to those of other studies in this series that utilized more traditional, paper-based questionnaires.

Surgical Influence: How Does Major Abdominal Surgery Influence Appetite?

The influence of different surgical procedures on postoperative appetite is manifold.

TABLE 1. Methods of Measuring Appetite or Appetite Loss

Appetite Measurement Instrument	Description	Reference	Appetite Question	Answering Options	Recommended Field of Use
Quality of life questionnaire of the European Organization for Research in the Treatment of Cancer (EORTC QLQ-C30)	30-item questionnaire reflecting multiple dimensions of quality of life, one of them being appetite loss.	Aaronson et al 1993[57]	During the past week: Have you lacked appetite?	Four-point Likert scale: Not at all, A little, Quite a bit, Very much.	Appetite measurement in a longitudinal follow-up of cancer surgery patients due to the multiple dimensions of quality of life in the questionnaire.
Visual analog scales assessing appetite sensation in single test meal studies	13 item questionnaire; all items visual analog scales 4 of them on appetite	Flint et al 2000[58]	How hungry do you feel? How satisfied do you feel? How full do you feel? How much do you think you can eat?	Four 100 mm visual analog scales.	Investigations specifically focusing on changes in food consumption after surgery or medical interventions due to the multiple dimensions of appetite in the questionnaire
Time to first feeling of hunger	Patients are asked to report when they feel hungry for the first time after surgery.	Not validated. Examples of use include[86,88,89,102]	Are you hungry?	Yes/no	Investigation of enhanced recovery after surgery programs due to the relevance in a hospital setting and the ease of measurement and documentation by nursing staff.
Other questionnaires	Diverse	Diverse	Diverse	Diverse	Should not be used when appetite loss is in focus, but may be used for specific research questions that cover appetite as a secondary endpoint.
Custom scales	Custom tools including visual analog scales, Likert scales, or interviews on appetite loss	Diverse	Diverse	Diverse	Not recommended, because they are not standardized, comparable, or validated, especially if custom questions are used.

Patients reported appetite reduction or complete absence of appetite for weeks after esophageal resection.[43] As early as 1967, Adams found lack of appetite and absence of hunger as important reasons for suboptimal dietary intake in a series of 20 patients who survived at least 1 year after total gastrectomy for benign or malign indications.[64] In colorectal surgery, appetite loss was reported generally rather mild.[65] On a population-based level, 65% of patients suffer from appetite loss after pancreaticoduodenectomy for pancreatic adenocarcinoma.[66]

Given the complexity of surgical influence on appetite loss and the numerous publications describing this issue, we focused the remaining parts of this paper on treatment options for surgical practice. However, Supplemental Digital Content 2, http://links.lww.com/SLA/D655 gives a detailed overview of the influence of different types of surgery on postoperative appetite loss described in 85 of the studies found in this systematic review.

Treatment: Pharmacological Treatment of Postoperative Appetite Loss

Various pharmacological treatment options of postoperative appetite loss have been described,[67–81] but high-level evidence is limited. In the following, we will give a brief overview of the treatment options described in the literature. In addition, Table 2 summarizes mechanism of action, formulation, advantages disadvantages, and types of surgery for which the respective substance has been studied. A detailed description of the available evidence obtained from 30 of the studies found in this systematic review can be found in Supplemental Digital Content 3, http://links.lww.com/SLA/D656.

Peripherally acting μ-opioid antagonist Alvimopan has been shown to have a positive influence on (lower) gastrointestinal function, but the effect on appetite remains questionable.[70] 5-hydroxytrypta-mine 4 (5-HT4)-receptor-agonist mosapride citrate showed a nonsignificant trend toward restoration of preoperative appetite after distal gastrectomy.[72]

TABLE 2. Overview of Pharmacological Treatment Options for Appetite Loss. Due to Lack of Evidence, Steroids Are Not Listed

Active Substance	Mechanism of Action	Formulation	Advantages	Disadvantages	Positive Effects on Appetite	No effect on Appetite
Alvimopan	Antagonist of peripheral μ-opioid receptor	Orally, 12 mg twice a day starting the day before surgery	Shortens time to return of bowel function	Appetite not measured in trials.	Bowel resection, cystectomy, hysterectomy[67-70]	Bowel resection, hysterectomy[71]
Mosaprid citrate	5-HT4-receptor-agonist improving gastrointestinal motility	Orally, 15 mg per day	Long-term treatment possible.	No randomized, controlled evidence.	Distal gastrectomy with pouch reconstruction[72]	
Octreotid	Attenuation of satiety gut hormone signals to the brain.	Subcutaneously, 100 μg		Very limited evidence	Esophagectomy[73]	
Dronabinol	Activation of cannabinoid 1 receptor in the brain stimulates appetite	Orally, 2.5 mg (=0.1 mL) on a sugar cube. A daily dose of 10 mg is usually sufficient	Easy application	Restrictions in use of cannabinoids by governmental bodies	Not investigated in surgery	Not investigated in surgery
Ghrelin	Endogenous hormone for central nervous appetite stimulation	Intravenously, 3 μg/kg twice daily	Direct appetite stimulation	Only intravenous administration studied in surgical patients. Only phase II trials.	Gastrectomy,[74,76] esophagectomy[75]	Gastrectomy,[77,78] esophagectomy[78]
Rikkunshito	Increase of plasma ghrelin levels	Orally, 2.5 g 3 times daily	Long-term treatment possible	No randomized, controlled evidence.	Gastrectomy[79,8O]	Esophagectomy[81]

5-HT4 indicates 5-hydroxytryptamine 4.

Octreotid had no positive influence on appetite 2.5 years after esophagectomy.[73] Cannabinoids[82] and corticosteroids, which are appetite stimulants known from palliative medicine, have not been investigated in surgical patients. For the "appetite hormone" ghrelin (see further section on etiology of appetite loss) synthetic i.v. application leads to an improved appetite in the immediate postoperative period,[74] but not in the long-term.[77] However, despite the availability of randomized controlled trials, quantitative data synthesis for ghrelin was not possible because of the heterogeneity of measurement endpoints, ghrelin treatment protocols, and time since operation. Moreover, because ghrelin has only been studied in phase II trials thus far, it is not available for routine use. The traditional Japanese herbal medicine Rikkunshito has been reported to improve postoperative appetite after gastrointestinal surgery by increasing plasma ghrelin levels[79] and as having positive effects on cancer-related symptoms.[83]

Treatment: Nonpharmacological Treatment of Postoperative Appetite Loss

Digitalized Interventions

Gustavell et al used an application for symptom self-reporting, graphic documentation, risk alerts, and access to self-care advice. It improved appetite loss and other common symptoms at 6 weeks after pancreaticoduodenectomy, but no longer had an impact on appetite loss 6 months after surgery.[84]

Evans et al described a rather unconventional phenomenon that patients who watched cooking shows had a significantly faster return of appetite after surgery than patients who did not. Surgeons can recommend this uncomplicated method to their patients without further concerns.[85]

Gum Chewing

Daily gum chewing 3 times for 1 hour each after sigmoid surgery reduced time to first flatus and bowel movement and length of hospital stay, but not time to first feeling of hunger in a randomized controlled trial of patients after open sigmoid surgery.[86] Another randomized controlled trial in which chewing gum containing sugar was used 3 times daily, for 45 minutes each for 7 days (compared to no chewing gum) after colorectal surgery, found no change in appetite, but an increased incidence in bloating, indigestion, and eructation in the chewing gum group.[87] In a third randomized controlled trial with gum chewing 3 times a day from day 1 until discharge after colorectal surgery, time to feeling hungry, time to first flatus and first bowel movement, but not length of hospital stay were shorter for the gum chewing group overall, with effects being even more pronounced in the colonic resection sub group.[60] In a randomized controlled trial of patients with laparotomy for ileostomy closure after typhoid perforation peritonitis, patients who chewed gum 3 times a day for 1 hour had a shorter time to return of hunger, first flatus, and first bowel movement than those who did not.[88] Another randomized controlled trial in patients with open or laparo-scopic colonic resection failed to show any benefits of gum chewing, but was also likely underpowered, due to the introduction of Alvimopan into routine care midway through the trial, which led to the exclusion of many patients.[89]

A meta-analysis of the available randomized controlled data (Fig. 5 top) showed that gum chewing reduces time to first hunger in patients after bowel surgery by 21.2 hours (95% confidence interval 28.77 to 13.65 hours). The trial by Zaghiyan et al was not included in the meta-analysis, because time to first hunger was not reported. Risk of bias assessment revealed a low risk of bias for the studies (Fig. 5 bottom). Thus gum chewing might help to improve appetite in other surgical patients, as well.

Nutritional Interventions

A recent systematic review on oral nutritional interventions in patients undergoing gastrointestinal surgery for cancer reported inconsistent findings and little evidence for the benefit of nutritional support, but the problem of appetite loss was not addressed.[90]

A review on nutritional interventions after pancreatic surgery recommended treating appetite loss with liquid supplements, 8–10 very small meals per day, and no zero or low-calorie foods.[91]

Preoperative oral carbohydrates failed to improve appetite (as measured by a hunger VAS) over the first 2 days after colorectal surgery.[92] Postoperatively, patients who had open or laparoscopic colorectal surgery mostly preferred small portions

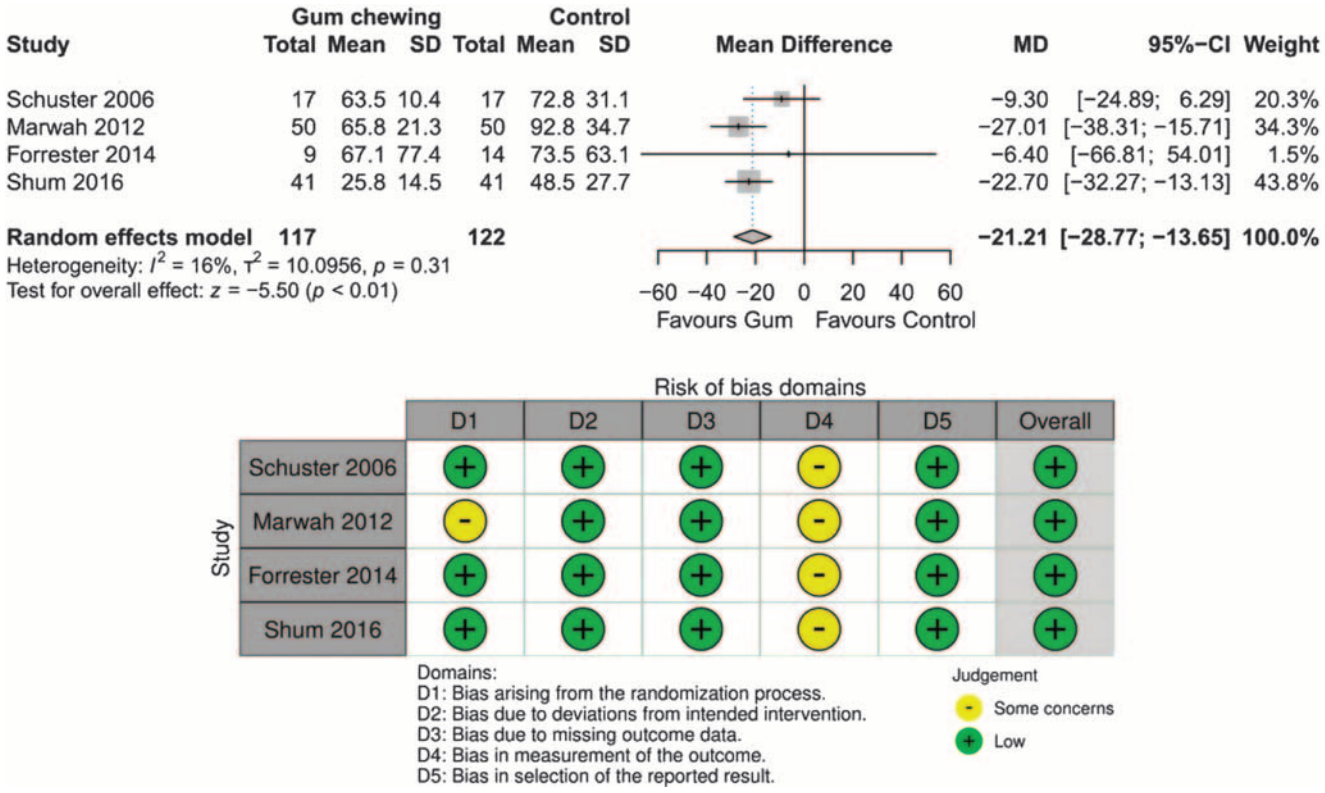

FIGURE 5. Meta-analysis for time to first hunger with gum chewing as an intervention. Forest plot (top) and risk of bias assessment (bottom).

of simple foods such as broth, soup, eggs, and toast and fresh fruit, coffee/tea, and ice cream rather than a clear-fluid diet as their first postoperative meal, even if they had low hunger (76% of patients).[93]

Appetite loss was significantly reduced after discharge from the hospital, according to a meta-analysis of 9 randomized controlled trials comparing home enteral nutrition to an oral diet after esophagectomy for esophageal cancer[94] (this analysis included a study by Wu et al that has also been included in our review). This study, however, reported significantly less appetite loss after 3 months in a group of patients who underwent minimally invasive surgery with home enteral nutrition versus those who had an open esophagectomy, with no significant difference between the groups 2 weeks postdischarge.[95] Thus it is unclear whether these changes can be attributed to the use of home enteral nutrition or to minimally invasive surgery. Another randomized controlled trial investigated the effects of oral nutritional supplements with dietary advice versus dietary advice alone for 3 months after surgery for gastric cancer and positive screening for nutritional risks. The authors found that oral nutritional supplements resulted in less appetite loss.[96]

Enhanced Recovery After Surgery

It is well known that early postoperative feeding is beneficial for surgical patients. This is despite their decrease in appetite if undertaken in a multimodal approach, often summarized as enhanced recovery after surgery or fast-track surgery, but not if enforced feeding alone is applied.[97]

A multimodal concept of enhanced recovery after surgery has been shown to improve the rate of reduced appetite in hepatocellular carcinoma liver resection patients.[98] In a randomized controlled trial for patients undergoing laparoscopic distal gastrectomy, a fast-track program was found to improve appetite loss, among other parameters. This program included intensive preoperative education, a short duration of fasting, preoperative carbohydrate loading, early postoperative ambulation, early feeding, and a preperitoneal local anesthesia pumping device.[99] Patients after open colonic surgery for cancer undergoing an enhanced recovery after surgery program reported significantly less appetite loss on days 3, 6, and 10, but same appetite loss 14, 21, and 28 days after surgery compared to patients undergoing conventional management.[100] Here, the program included no mechanical bowel preparation, no preoperative fasting, early postoperative feeding, restricted intravenous fluids, and early mobilization.

A similar practice that falls under the umbrella of "high-quality nursing" improved appetite and quality of life in a randomized controlled trial in postoperative liver cancer patients. The practice included, among other interventions, health education and nutritional intervention before surgery, postoperative mood control, postoperative diet intervention, and family nursing and healthcare.[101]

Some authors consider enforced feeding unpleasant for patients and advocate resuming feeding based on the patient's appetite.[102] However, even in a setting of enhanced recovery after surgery, loss of appetite is the number 1 reason for missed meals[103] or patients' self-perceived barriers to sufficient nutrition.[104] Thus enhanced recovery after surgery may improve, but does not solve the problem of appetite loss.

Postdischarge Counselling

Chasen et al reported their experience with a multidisciplinary interventional rehabilitation program for patients with gastroesoph-ageal cancer. This program included physicians, oncology nurses, dieticians, physical and occupational therapists, social workers, and psychologists. Appetite, among other factors, improved over the program's 8-week duration.[105] However, the authors did not state which proportion of their patients underwent surgery before participating in the program.

Pinto et al investigated the benefits of nutritional and/or respiratory counseling after esophagectomy for cancer in a randomized controlled trial with 4 treatment arms covering the period from before surgery until 3 months after discharge. Nutritional counseling improved appetite loss 1 month but not 3 months after discharge, but neither nutritional nor respiratory counseling improved quality of life.[106]

In summary, multidisciplinary support and advice may improve appetite after discharge from the hospital.

DISCUSSION

Summary of Evidence

Appetite loss is an important clinical problem after major abdominal surgery. Especially in the case of esophageal and gastric surgery, numerous studies have described persistent appetite loss, even with long-term follow-up, and mostly in the context of quality of life assessment. After colorectal surgery, the problem of long-term appetite loss may be less pronounced, but it is nevertheless relevant in the days and weeks immediately after surgery. After pancreatic surgery, appetite loss is a common problem that may persist, especially if upper gastrointestinal anatomy and physiology are altered by pancreaticoduodenectomy.

The evidence regarding treatment of appetite loss after major abdominal surgery is limited, rendering it an unsolved problem. The only level IA evidence found in this review was the reduction of time to first hunger due to gum chewing after bowel surgery. Alvimopan reduces postoperative ileus, thus possibly reducing appetite loss, but this endpoint has not been investigated. 5-HT4-receptor agonists increase gastrointestinal motility, but their ability to improve appetite loss has only been investigated by a single study, and with insignificant results. The same is true for Octreotid. Only the treatment of appetite loss with ghrelin has been studied more extensively, probably due to its established and important role in appetite regulation and known changes in ghrelin levels after upper gastrointestinal surgery. However, evidence is limited to phase II trials within gastric and esophageal surgery. Also, until now, only intravenous administration has been investigated in surgical patients. Rikkunshito, the herbal stimulant of ghrelin secretion, has also been studied, but investigations of novel oral ghrelin agonists such as Anamorelin have been limited to nonsurgical patients, for example, those with cancer-related cachexia.[107] The same is true for other well-known appetite stimulants: cannabinoids, steroids, and megestrol acetate[108] have been neglected in surgical research as potential treatments for postoperative appetite loss.

The nonpharmacological treatment of postoperative appetite loss can be subsumed under the term "multidisciplinary and multimodal support," both in hospital, in the form of enhanced recovery after surgery, and after discharge, via nutritional counseling. Two exceptions include gum chewing, which has been shown to reduce time to initial hunger among colorectal surgery patients, and watching cooking shows, which can stimulate appetite. Every surgeon can easily recommend both of these interventions during morning rounds.

Limitations

The studies reported in this review are highly heterogenous with respect to patient population, intervention type, outcome measurement methods, and evidence levels. For example, it is difficult to determine if the authors differentiate between appetite and hunger, as both terms are used synonymously in some studies while others only use one of them. Therefore, the evidence must be interpreted carefully and the primary studies appraised critically. Furthermore, this review is at risk of confirmation bias. Articles were screened primarily for the terms "appetite" or "hunger." Thus our search was likely to include studies reporting appetite loss when assessing patient populations with the EORTC QLQ-C30 questionnaire, for example, whereas abstracts of studies not reporting appetite loss may have been excluded unintentionally, because they did not mention the appetite loss subscale at all. Nevertheless, the sheer number of studies found—and included—in this review proves how relevant a problem appetite loss is, and how this issue reflects the daily reality of major abdominal surgery practice.

Also, the EORTC QLQ-C30 has been designed and used primarily for cancer patients. But the problem of postoperative appetite loss is not limited to cancer patients, but also patients receiving gastric surgery for ulcer being refractory to conservative treatment or pancreatic resection for precancerous lesions such as IPMN. Furthermore, it is not detailed enough to investigate the different layers of appetite loss for a better understanding of the problem after major abdominal surgery. Thus, novel ways of measuring appetite need to be established.

Similarly, we excluded publications on metabolic surgery from this review, because here appetite loss is intentional and desired. Nonetheless, the research investigating the role of not only hormonal changes, but also gut microbiota and bile acid reversal after metabolic surgery may help to understand the undesired changes in appetite after nonmetabolic abdominal operations.[109] The faster passage of food through the upper gastrointestinal tract is similar in esophageal surgery for cancer and sleeve gastrectomy for obesity because the stomach is cut into a sleeve shape in both operations. The effects of sleeve gastrectomy on rapid gastric emptying can also be used to treat gastric paresis.[110] The hormonal changes after sleeve gastrectomy have been extensively studied and are likely due to the fast gastric emptying.[111,112] Gastric bypass is similar to gastrectomy as Mason and Ito stated already in 1967.[18] Furthermore, GLP1-secretion from the jejunum and ileum increases after metabolic surgery due to the anatomical changes and more nutrients reaching the GLP-1 secreting cells in the jejunum and ileum. Such changes occur after every type of small bowel resection because the number of L-cells secreting GLP-1 increase toward the end of the ileum. The many effects of GLP-1 on appetite and intestinal and pancreatic hormone secretion leads to appetite loss and have been described elsewhere.[113] Nevertheless, it remains unclear how GLP1-secretion changes after pancreatic resections or colorectal surgery. In addition, changes in bile acid secretion and interactions between bile acids and the microbiome contribute very likely as well to the changes in appetite and gastrointestinal function.[114] Also, we do know, that the patients response to surgical trauma is also influenced by postoperative nutrition and mediated by endogenous glucagon-secretion,[115] but it remains unclear whether the change in the insulin, glucagon, and the whole neuroendocrine system experienced after metabolic surgery[116] influences postoperative appetite loss in other surgical patients as well.

Implications for Further Research

This review revealed several opportunities for further investigation of the problem of appetite loss after major abdominal surgery, namely: Is appetite loss "normal" in the immediate postoperative period? Is it negligible compared to other, more objective symptoms such as postoperative ileus or subjective but more severe ones, such as pain? Can we apply surgically investigated appetite stimulants more broadly? Can we apply other appetite stimulants in surgery? First, the baseline of appetite loss after abdominal surgery should be more closely investigated. Similar to studies in orthopedic surgery,[17] this would allow for estimating the effect of surgical trauma itself in contrast to long-term alterations in gastrointestinal anatomy and physiology.

Second, the few treatment options that have been investigated in limited surgical areas (phase II trials of ghrelin in upper gastrointestinal surgery, Rikkunshito in esophageal and gastric surgery, gum chewing, and Alvimopan in colorectal surgery) should be investigated in other types of major abdominal surgery. Unconventional treatment options such as watching cooking shows should be prospectively investigated, maybe even in a setting of virtual reality simulations that introduce even more immersion and may increase effects. Although associated with increased treatment effort, a multimodal concept of enhanced recovery after surgery also seems promising. Preliminary results point toward increased appetite after the use of preoperative health education, nutritional intervention, early feeding, and postoperative mood control. Future studies should investigate the efficiency of enhanced recovery programs for different types of surgical interventions. This should include investigation of prehabilitation with a low-fat/high-fiber diet as this may lead to changes in the gut microbiome, which has improved postoperative bowel movement in preclinical studies and may also improve postoperative appetite loss.[117]

Third, because most studies measured appetite via self-report measures on a 4-point Likert scale summarizing the past week designed for cancer patients (EORTC QLQ C30), a more precise assessment of appetite and food intake may offer additional insight into the etiology and progression of postoperative appetite loss also for nononcological patients. Measuring the current, momentary sensation of appetite in a natural setting and in greater detail may also provide a more accurate index of physiological, gustatory, and psychological changes in appetite than the above-mentioned questionnaires administered in the outpatient clinic. Behavioral sampling techniques that assess appetite in "real time," such as the "Ecological Momentary Assessment," have been previously used to assess everyday appetite in healthy individuals and patients with eating disorders.[118–120]

Finally, surgeons should learn from their colleagues in medical oncology and palliative medicine, and investigate the efficacy of well-known appetite stimulants (eg, cannabinoids, steroids, meges-trol acetate) in the treatment of short-term and long-term appetite loss after major abdominal surgery.

Appetite loss after major abdominal surgery is a common problem with prognostic relevance. Its etiology is complex and multifactorial. Evidence regarding the effective treatment of postoperative appetite loss is limited. Moving forward, surgical trials should include the assessment of appetite loss as a relevant outcome parameter.

ACKNOWLEDGMENTS

The authors thank Elisabeth Corrao-Billeter for reviewing the manuscript as a native speaker.

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